MEDICAL PROCEEDINGS
MEDIESE BYDRAES

A South African Journal for the Advancement of Medical Science

'n Suid-Afrikaanse Tydskrif vir die Bevordering van die Geneeskunde

Registered at the General Post Office as a Newspaper — By die Hoofposkantoor as Nuusblad Geregistreer

Vol. 1 • No. 4 • 5s | Johannesburg Oktober 1955 October | Jaarliks £1 : 1 : 0 Yearly

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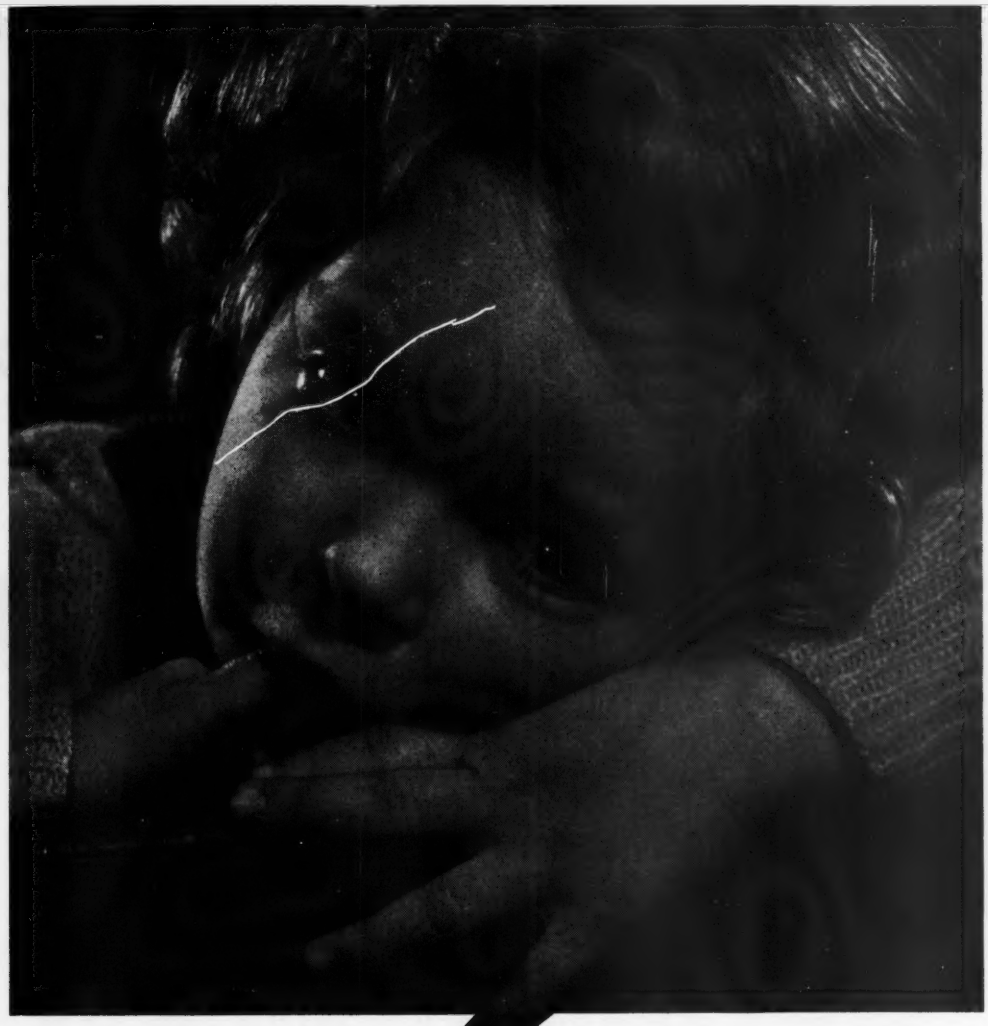

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Medical Proceedings · Mediese Bydraes

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VOL. II, No. 8 1955

ANTIBIOTIC NEWS AND NOTES

GERMANY: TERRAMYCIN* (brand of oxytetracycline) "BROADLY EFFECTIVE" IN OSTEOMYELITIS - In osteomyelitis "the advantages of Terramycin...lie in the possibility of intravenous administration (in diseases endangering life) as well as in the broad range of effectiveness...." Weber treated with Terramycin 23 children with acute hematogenous osteomyelitis, 13 patients with chronic bone suppuration from war injuries. Children treated on the second to fourth day of illness showed a "course of recovery without complications." In those admitted on the seventh to tenth day with periosteal abscesses, the surgical course was considerably shortened. In patients with chronic suppuration, healing without pyrexia was observed. Children were given Terramycin intravenously and orally and chronic suppuration was treated with oral Terramycin and local application of Terramycin in sterile saline solution.

Weber, F.: Med. Klin. 50:669 (April 15) 1955.

AUSTRIA: VIOMYCIN "LIFESAVING" IN RESISTANT TB - Viocin* (brand of viomycin sulfate) treatment of patients with advanced tb resistant to streptomycin and INH "as a whole must be described as satisfactory," according to Austrian clinicians. "In some patients Viocin was a lifesaver since there seemed to be no possibility of an effective treatment." Viocin was used in 48 patients in combination with other tb medications. Dosage: 2 Gm. daily to maximum of 50 Gm.

Balogh, A.: Wien. med. Wchnschr. 105:266 (April 2) 1955.

GERMANY: COMBINED PENICILLIN-STREPTOMYCIN PREFERRED IN ENDOCARDITIS- In endocarditis lenta "penicillin-streptomycin treatment is superior not only purely numerically ...but also when the initial condition is considered." In 24 cases so treated success was obtained in 17 (70%) without regard to severity of initial findings. Of 23 cases treated with penicillin alone, success was obtained in 10. "Success in treatment depended to a large extent on the initial findings whereas dosage and length of treatment seemed to have a slighter influence on the result."

Krauel, G.: Medizinische No. 19:703 (May 7) 1955.

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TERRAMYCIN IN CLINICAL MEDICINE

Part I of a recent symposium on New Facts and Perspectives of Broad-Spectrum Antibiotic Therapy was devoted to the use of Terramycin* (brand of oxytetracycline) in clinical medicine. Among the papers presented:

BONE, JOINT AND SOFT TISSUE INFECTIONS - In treatment of acute lesions, Buchman (Hosp. for Joint Disease) recommends that Terramycin be given "as promptly as possible" in doses of 500 mg. orally four times daily. For very ill patients, an initial dose of 500 mg. intravenously or an intramuscular injection "will produce an adequate blood level promptly." If there is no response after 72 hours (at the most) surgery is indicated. Chronic lesions should be treated surgically, with adjunctive antibiotics. The author administers 500 mg. of Terramycin orally every 6 hours for 24 hours preoperatively. During surgery, 500 mg. are given intravenously. The wound is thoroughly washed and flooded with a solution of normal saline containing 0.5 mg. of Terramycin/ml. diluent. Postoperatively, the patient receives 500 mg. by mouth four times daily for about four weeks. With the use of this technique the author "has been able to obtain 80 to 90 per cent primary closures with an insignificant rate of recurrences in a period of observation ranging up to 10 years." "Gratifying results" follow the use of Terramycin in the treatment of compound fractures, compound dislocations, and wounds of the soft tissues. Treatment is similar to that outlined for chronic infections.

Buchman, J.: Internat. Rec. Med. 168:213 (April) 1955.

GONORRHEA - Terramycin Intramuscular "is effective in the treatment of acute gonorrhea," report Marmell and Prigot (Harlem Hosp.). To prevent relapse, the minimal total dosage should be 400 mg. The authors gave two simultaneous injections of 100 mg. on two sucessive days to eight patients; cure was obtained in seven. "No drug toxicity of any sort was observed in any of our patients," and none complained of "undue pain."

Marmell, M., and Prigot, A.: Internat. Rec. Med. 168:254 (April) 1955.

DERMATOLOGY AND SYPHILOLOGY - Terramycin is a "valuable addition" to drugs used in treating skin diseases, in the opinion of Robinson. He reports results in 1706 patients. Terramycin ointment† is "of definite value" in pyodermas (1016 patients), causing rapid healing, e.g. in impetigo contagiosa and ecthyma. Oral Terramycin is of definite benefit in all conditions of which pyogenic organisms are the primary cause and in treating secondary pyogenic invasion of dermatoses. Granuloma inguinale healed rapidly under oral Terramycin treatment, with no relapses. Erythema multiforme responded in 17 of 24 cases. Terramycin is a valuable adjunct to syphilotherapy and should be used in penicillin-sensitive individuals.

Robinson, H. N., Jr.: Internat. Rec. Med. 168:207 (April) 1955.

GYNECOLOGY AND OBSTETRICS - Terramycin* (brand of oxytetracycline) "has a very definite place in the practice of obstetrics for both obstetric infections themselves and for some infections incidental or related to pregnancy," states

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†Available as Terramycin Topical Ointment with Polymyxin B Sulfate, containing 30 mg. Terramycin and 10,000 polymyxin B sulfate per gram. For combating superficial inflammation and coexisting or potential infection Terra-Cortril* Topical Ointment is also available, containing 1.0% (10 mg.) of hydrocortisone and 3.0% (30 mg.) of Terramycin per gram.

Hesseltine.[1] It "has a broad coverage and has rarely produced sensitization in patients, and bacteria seem less likely to develop resistance to it." He reports use in endometritis, intussusception, pyelitis in postpartum patients, pointing out that "incidental, nonobstetric infections must be expected in pregnant women about as often as in the nonpregnant." According to Blinick and Soichet,[2] Terramycin has proved effective in many gynecologic conditions, including bartholinitis, chancre, chancroid, granuloma inguinale, acute and chronic cervicitis and wound infections. In postoperative wound infections, when isolation and sensitivity testing are not feasible, Terramycin "used empirically often gives dramatic results." Authors have also satisfactorily used Terramycin vaginal suppositories* for vaginal antisepsis prior to total abdominal hysterectomy and vaginal operations.

1. Hesseltine, H. C.: Internat. Rec. Med. 168:229 (April) 1955.
2. Blinick, G., and Soichet, S.: Ibid., p. 238.

GENITOURINARY INFECTIONS - Terramycin "is an antibiotic of proved worth in the treatment of infections of the genitourinary tract." If used in a "logical" fashion, it "may be expected to cure the majority of acute infections caused by organisms sensitive to it...." Baum (University Hosp., Ann Arbor, Mich.) finds that an initial loading dose of 1.0 Gm. and 250 mg. every 6 hours will maintain relatively high blood levels. In most instances 2.0 Gm./day for five to seven days "is sufficient" to resolve the infections. Patients unable to accept oral medication may be given Terramycin intravenously in dosage of 0.5-1.0 Gm. twice daily.

Baum, W. C.: Internat. Rec. Med. 168:248 (April) 1955.

SURGERY - That Terramycin "has wide applicability of great value as an adjunct in the surgical management of peritonitis and peritoneal contamination is beyond question," state Prigot and Maynard. With broad-spectrums "death from uncontrolled peritonitis in acute surgical emergencies has been reduced to negligible proportions." Terramycin was given intravenously and orally to 88 patients with established peritonitis caused by appendicitis, perforated ulcer, ruptured gastric carcinoma or rectal diverticulum. The post-operative course was "especially gratifying" and "remarkable." Within 36 hours patients were comfortable and recovery was uninterrupted. Terramycin also prevented peritonitis in 26 patients with peritoneal contamination. Postoperative course in all cases was "eminently satisfactory." Dosage: Intravenous, 500 mg. Terramycin twice daily for 2-3 days; oral, 1-2 Gm. daily for 7-8 days.

Prigot, A., and Maynard, A. de L.: Internat. Rec. Med. 168:220 (April) 1955.

STEROID STUDIES

HYDROCORTISONE VALUABLE IN DERMATOLOGY - Cortril† (brand of hydrocortisone) Topical Ointment, 2.5%, 1.0% or 0.5%, when used alone, is "an adequate, effective therapeutic agent" in mild forms of contact dermatitis, transient flares of atopic dermatitis, infantile eczema, uncomplicated stasis dermatitis, some cases of idiopathic pruritus vulvae and pruritus ani, in the opinion of Welsh and Ede. Cortril Ointment is also "a valuable adjuvant to therapy" in very acute or chronic forms of: atopic dermatitis, contact dermatitis, localized neurodermatitis with lichenification, endogenous infectious eczematoid dermatitis, stasis dermatitis, psoriasis with complicating contact factors, other dermatoses complicated by allergic, chemical or

*Available as Terramycin Vaginal Tablets with Polymyxin B.
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bacterial factors. Authors have observed the response of 708 patients to hydrocortisone, both acetate and free alcohol, find the free alcohol more effective. In very acute dermatoses or in chronic dermatoses with lichenification, the 2.5% ointment is required, otherwise they believe the lower concentrations are adequate. Relapse is minimal when Cortril Ointment is used adjunctively. "Increased tolerance to other topical agents occurred in patients in whom hydrocortisone was used concomitantly."

Welsh, A. L., and Ede, M.: Ohio State M. J. 51:350 (April) 1955.

ARGENTINA: TOPICAL HYDROCORTISONE ACTS ON KELOIDS - Flat keloids in 6 patients were treated topically with 1% hydrocortisone ointment three times daily for a number of months by Mancini and Stringa (Inst. Nacional de Endocrinologia, Buenos Aires). Itching disappeared after the first week, congestion decreased after two months and the keloids atrophied in four to six months. Biopsies showed progressive decrease in tissue hyperplasia, no changes in cutaneous epithelium. Biopsies carried out during treatment did not cause abnormal scars. Similar treatment of hypertrophic scars resulted in only minimal changes.

Mancini, R. E., and Stringa, S.: Paper read by title to the Endocrine Society, 37th Meeting, Atlantic City, June 2-4, 1955 (Program Abstract).

GENERAL MEDICINE

NEW STEROID ANESTHETIC ANNOUNCED - Viadril* (brand of hydroxydione), an intravenous anesthetic, chemically a steroid, but without hormonal effects, has recently been announced in the U.S. and Switzerland. Murphy, Guadagni and DeBon (University of California), who have used Viadril in 125 operations of all types, conclude "that it is a true anesthetic agent as evidenced by its ability to control pain, obtund reflexes, produce relaxation and produce sleep, all without depression of vital functions." Most satisfactory results were obtained with a combination of Viadril with 3:1 nitrous oxide-oxygen. "Viadril has given nitrous oxide the added potency to make it an adequate anesthetic without detracting from its safety and controllability." In the lightly premedicated patient Viadril produced sleep in 5-10 minutes - "a smooth, quiet process devoid of any excitement phase." In 96% of the patients, operations lasted more than one hour; in these 1.0-1.5 Gm. Viadril were used. Maximum effect was produced for about two hours. In patients requiring intratracheal intubation (91), it was usually easily possible to intubate without relaxants, once Viadril sedation was effective. When relaxants, meperidine or other anesthetics were thought necessary, dosages were considerably less than those required with thiopental. Most patients (80%) were responsive at the end of the procedures. It is the authors' "firm clinical impression" that Viadril "produced a definite analgesic state far greater than that produced by the barbiturates."

Murphy, F. J.; Guadagni, N. P., and DeBon, F. L.: Papers presented before the International Surgical Congress, Geneva, May 24, 1955; and American Medical Association, 104th Annual Meeting, Atlantic City, June 8, 1955.

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1. Sulzberger, M. B., *et al.: J.A.M.A.* **151**:468, Feb. 7, 1953.
2. Smith, C. C.: *A.M.A. Arch. Dermat. & Syph.* **68**:50, July 1953.

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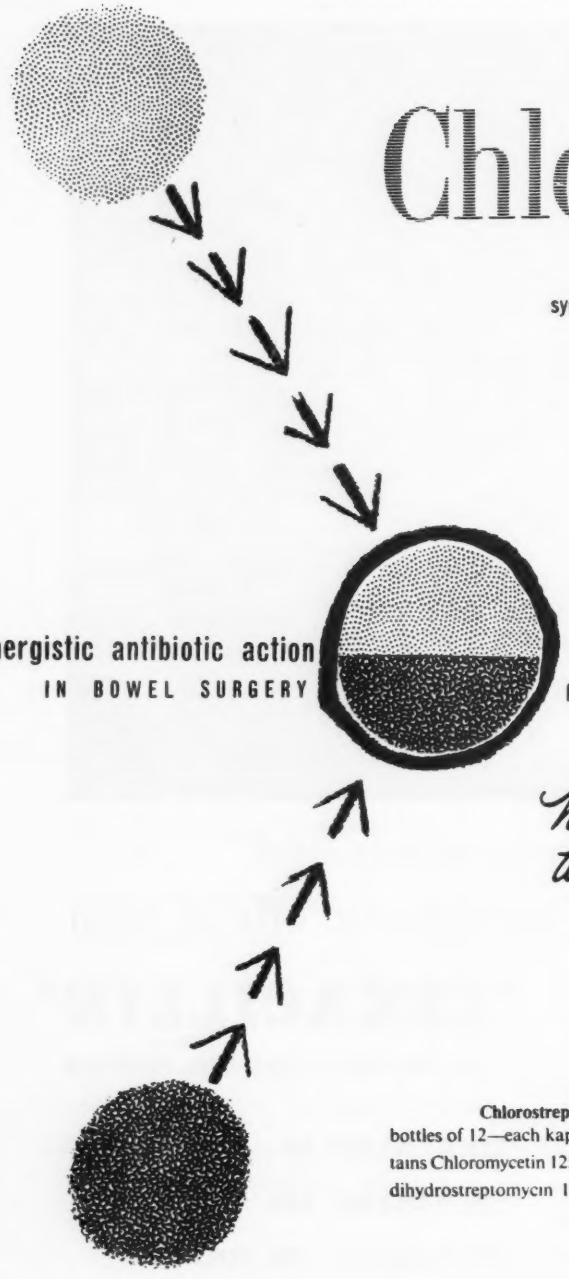

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A South African Journal for the Advancement of Medical Science

'n Suid-Afrikaanse Tydskrif vir die Bevordering van die Geneeskunde

P.O. Box 1010 · Johannesburg

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Vol. I | Oktober 1955 October | No. 4

REDAKSIONEEL

DIE PROBLEEM VAN INENTING TEEN POLIOMIËLITIS

Ten gevolge van spesiale reëlings wat met die Nasionale Stigting vir Kinderverlamming in New York getref is, is ons in staat om die jongste versameling inligting oor die Salk-entstof aan mediese praktisyns in die Unie voor te lê. Die referate is geredigeer deur dr. Hart E. van Riper, mediese direkteur van die Stigting, en is slegs sowat 8 weke gelede tot beskikking van ons Amerikaanse kollegas gestel.

Die afwyking van ons normale publikasiegewoontes word geregverdig deur die belangrikheid van die aangeleentheid in Suid-Afrika waar 'n vernietigde entstof van die Salk-tipe vrygestel is.

In sommige kringe sal die Amerikaanse gegewens waarskynlik as 'n partydige seleksie van materiaal beskou word. Dit is ongetwyfeld waar dat daar ernstige meningsverskille bestaan oor die teorie en die gebruik van 'n vernietigde entstof. Enders (aan wie die Nobel-prys toegeken is vir sy werk in verband met die poliomiëlitisvirus), Hammond, van Pittsburgh ('n akademiese kollega van Salk) en Sabin (wat 'n voortreflike bydrae gelewer het tot die produksie van verswakte lewende poliomiëlitisvirus-entstowwe) was in 'n minderheid van 3 (teen 8) om inenting met die inaktiewe entstof stop te sit tot tyd en wyl dit konsekwent veilig gemaak kon word—'n posisie wat teen hierdie tyd waarskynlik in die Verenigde State bewerkstellig is, en bes moontlik die vorige besware van sulke vooraanstaande viroloë en epidemioloë uit die weg geruim het.

Aan die ander kant het dr. G. S. Wilson

EDITORIAL

THE PROBLEM OF VACCINATION AGAINST POLIOMYELITIS

We are able, as a result of special arrangements with the National Foundation for Infantile Paralysis in New York, to make available to medical practitioners in the Union the latest assembly of information on the Salk vaccine, edited by Dr. Hart E. van Riper, the Medical Director of the Foundation, and released to our American colleagues only some 8 weeks ago.

The interruption of our normal publishing schedule is warranted by the importance of the matter in South Africa where a killed vaccine of the Salk type has been released.

In some quarters the American data may be regarded as a partisan selection of material. It is undoubtedly true that opinion is divided, to a serious extent, on the theory and the use of a killed vaccine. Enders (awarded a Nobel prize for his work on the poliomyelitis virus), Hammond of Pittsburgh (an academic associate of Salk) and Sabin (who has made outstanding contributions in the production of attenuated living poliomyelitis virus vaccines) were in a minority of 3 (against 8) to stop inoculation with the inactivated vaccine until it could be made consistently safe—a position which has by now probably been achieved in the United States and which may, therefore, have rendered obsolete the previous objections from such eminent virologists and epidemiologists.

On the other hand, Dr. G. S. Wilson (Director of the Public Health Laboratory Services in the United Kingdom), has again drawn attention (in the *Brit. Med. J.*, 23 July 1955, p. 262) to the narrow margin between killing a

(direkteur van die Openbare Gesondheids-laboratorium in die Verenigde Koninkryk) weereens die aandag gevestig (in die *Brit. Med. J.*, 23 Julie 1955, bl. 262) op die enge grens tussen die vernietiging van 'n virus en die behoud van so 'n virus se vermoë om teenstowwe te vorm. Hy lê ook klem daarop dat die mens skynbaar meer gevoelig vir die virus as enige bekende dier is.

Daar moet ook besef word dat daar 'n denkrigting is wat, ondanks die ontleiding van die Salk-veldproefneming in die Francis-verslag, die mening toegedaan is dat geen vernietigde virus, bv. van beespokkies, geelkoors, ens., die bewys gelewer het dat dit in staat is om beskerming teen die onderskeie siektes op te bou nie, en verder dat die demonstrasie van neutraliserende teenstowwe wat onder eksperimentele toestande geproduseer is, nie noodwendig onvatbaarheid vir infeksie beteken nie.

Die ingewikkeldheid van die probleme waarvoor die praktisyn te staan kom wanneer ouers hom raad kom vra oor die inenting van hul kinders, word skerp deur hierdie faktore toegelig. Die gesaghebbende eerstehandse en oorspronklike dokumente wat nou vir die eerste keer in 'n maklik toeganklike vorm in Suid-Afrika beskikbaar gestel word, behoort ons kollegas heelwat te help om tot 'n beslissing oor hierdie belangrike aangeleentheid te geraak. Die Amerikaanse inligting wat in hierdie uitgawe gepubliseer word, handel onder meer ook oor sulke belangrike praktiese sake soos die posisie van die allergiese pasiënt, die tussenpose tussen inspuitings, die toedieningsroete, of daar tydens die poliomiëlitis-seisoen tot inenting oorgegaan moet word, die verwikkelinge wat deur swangerskap meegebring word, die kontra-indikasies vir inenting, die moontlike verband tussen antibiotica in die entstof en allergiese reaksies, en die moontlikheid van nierbeskadiging en die ontwikkeling van Rh-sensitisasie.

Die inligting wat deur die Stigting ingesamel is, word in hierdie uitgawe aangevul deur dr. G. Selzer se omvattende en ewewigtige oorsig van die praktiese aspekte van die siekte self. Dr. Selzer, wat aan die Virusnavorsingseenheid van die Universiteit van Kaapstad verbonde is, is by uitstek bevoegd om hierdie probleem te bespreek, aangesien sy reeds belangrike en fundamentele bydraes tot die studie van die poliomiëlitisvirus gelewer, en ook virusnavorsingswerk in die Rockefeller-instituut in Amerika gedoen het.

Die gewetensbesware en moeilikhede waaraan ons Oos-Londense kollegas onlangs uiting gegee het, was bloot 'n weerklank van die virus and retaining its antigenic powers. He also emphasized that the human species was evidently more sensitive to the virus than any animal known.

It must be recognized too that there is a school of thought which takes the view, despite the analysis of the Salk field trial in the Francis Report, that so far no killed virus, e.g. of vaccinia, yellow fever, etc., has been shown to be capable of inducing protection against the respective disease and further that the demonstration of neutralizing antibodies produced under experimental conditions does not necessarily spell immunity against infection.

These factors clearly outline the complexity of the problems which face the practitioner approached by parents for advice about the inoculation of their children. The authoritative first-hand and original documents which have been made available in an accessible form for the first time in South Africa should do much to assist our colleagues in making up their minds on this important issue. The American information published in this issue also deals, *inter alia*, with such very important practical matters as the position of the allergic patient, the spacing of injections, the route of administration, whether vaccination may be undertaken during the poliomyelitis season, the complications created by pregnancy, the contra-indications to inoculation, the relation of antibiotics in the vaccine to allergic reactions and the possibilities of kidney damage and the development of Rh sensitization.

The information gathered by the Foundation is further supplemented in this issue by Dr. G. Selzer's comprehensive and balanced review of the practical aspects of the disease itself. Dr. Selzer (writing from the Virus Research Unit of the University of Cape Town) is particularly qualified to deal with this problem as she has made important and fundamental contributions to the study of the poliomyelitis virus and has, in addition, done research work in the virus field at the Rockefeller Institute in America.

The conscientious doubts and difficulties recently expressed by our East London colleagues were merely an echo of what was felt very widely throughout the Union at the time. Medical practitioners can never be unmindful of their Hippocratic oath to 'abstain from harming or wronging any man' when using their powers to 'help the sick to the best of (their) ability and judgment'. The courageous stand of the East London practitioners in this matter is one which must have received strong moral support from almost all their colleagues

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destydse menings van baie geneeshere in alle dele van die Unie. Hul Hippokratiese eed om ‚hulle te weerhou daarvan om enige man kwaad te doen of te benadeel' wanneer hulle hul bevoegdheid gebruik ‚om die siekes tot die beste van (hul) vermoë en oordeel te help,' is iets wat mediese praktisyns nooit uit die oog durf verloor nie. Die dappere houding wat die Oos-Londense praktisyns in hierdie saak aangeneem het, het sekerlik die sterk morele steun van byna al hul kollegas geniet, en die optrede van die Minister wat hul grondige besorgdheid oor die probleem waarvoor hulle te staan gekom het, as ‚misleidend', ‚onverantwoordelik' en ‚kwaadwillig' beskryf het, word derhalwe betreur. Die verantwoordelikheid om 'n ouer aan te raai om 'n gesonde kind te laat inent, is 'n individuele verantwoordelikheid wat geen mediese praktisyn van hom kan afskuif nie, en wat iedere geneesheer as 'n gewetenssaak moet beskou. Vir hierdie doel moet hy *al* die beskikbare getuienis hê. Vorderings op die gebied van die geneeskunde word nie gemaak op las van 'n minister of op bevel van 'n staatsdepartement nie.

VIADRIL

'N NIE-BARBITURAAT-BINNEAARS-NARKOSE

Die kliniese belangrikheid van Selye se oorspronklike verslag in 1941[1] dat sekere steroïede (wat chemies aan progesteroon verwant is) chirurgiese anestesie by laboratoriumdiere te voorskyn kon bring, is blykbaar tot onlangs toe oor die hoof gesien. Emmens,[2] wat met onvolgroeide rotte gewerk het, het in 1947 Selye se aansprake ten opsigte van progesteroon en desoksikortikosteroon-asetaat beaam; maar hulle is hormoon-aktiewe stowwe, en Selye het ook die narkotiese eienskappe van hormoon-onaktiewe steroïede beskryf. Laasgenoemde was 'n uiters belangrike waarneming as hierdie nuwe kennis toegepas moes word op chirurgie by die mens. Dit was van fisiologiese belang dat steroïede, verwant aan progesteroon (wat 'n opvallend kalmerende effek op sekere soorte gladde spiere het) die bewys gelewer het dat dit 'n kalmerende effek op die sentrale senustelsel het, en dat dit van die hipnotiese na die anestetiese kan oorgaan, na gelang van die dosis wat toegedien word.

1. Selye, H. (1941): Proc. Soc. Exp. Biol. Med., N.Y., **46**, 142.
2. Emmens, C. W. (1946-1948): J. Endocrinol., **5**, xii.

and the action of the Minister in describing their genuine concern about the problem with which they were faced in such terms as 'misleading', 'irresponsible' and 'malicious', is to be deprecated. The responsibility of deciding to advise the inoculation of a healthy child is an individual one which no medical practitioner can avoid and which every practitioner must take upon his own conscience. For this purpose he must have *all* the available evidence. Advances in medicine do not proceed by Ministerial edict or Departmental ukase.

VIADRIL

A NON-BARBITURATE INTRAVENOUS ANAESTHETIC

The clinical significance of Selye's original report in 1941[1] that certain steroids (chemically related to progesterone) could produce surgical anaesthesia in laboratory animals was apparently overlooked until recently. Emmens,[2] working on immature rats, confirmed Selye's claims in 1947 in respect of progesterone and desoxycorticosterone acetate; but these are hormonally active substances whereas Selye had also described anaesthetic properties in hormonally inert steroids. The latter was a most important observation if this new knowledge was to be applied to surgery in Man. It is of physiological interest that steroids related to progesterone (which has a markedly sedative effect on certain types of smooth muscle) should also be found to have sedative effects on the central nervous system, progressing from the hypnotic to the anaesthetic, depending on the dose administered.

A short time ago Laubach *et al.*[3] (from the laboratories of Chas Pfizer & Co.) described 21-hydroxypregnanedione, a steriod devoid of hormonal activity, as an effective anaesthetic agent and at the recent Geneva meeting of the International College of Surgeons, Murphy *et al.* reported on 125 patients in whom this steroid (in the form of the hemi-succinate ester, i.e. Viadril) was used as the anaesthetic for some 20 different kinds of surgical procedure.

Viadril lacks oestrogenic, androgenic or ana-

1. Selye, H. (1941): Proc. Soc. Exp. Biol. Med., N.Y., **46**, 142.
2. Emmens, C. W. (1946-1948): J. Endocrinol., **5**, xii.
3. Laubach, G. D., P'an, S. Y. and Rudel, H. (1955): Brit. Med. J., **2**, 254.

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'n Rukkie gelede het Laubach *et al.*[3] (van die laboratoriums van Chas. Pfizer & Kie.) 21-hidroksipregnanedioon, 'n steroïed sonder hormoonaktiwiteit, beskryf as 'n doeltreffende verdowingsmiddel, en op die onlangse vergadering van die Internasionale Kollege van Chirurge in Geneve het Murphy *et al.* verslag gedoen oor 125 pasiënte by wie hierdie steroïed (in die vorm van die hemi-suksinaatester, d.w.s. Viadril) as 'n verdowingsmiddel gebruik is vir ongeveer 20 verskillende soorte chirurgiese prosedures.

Viadril het geen estrogeniese, androgeniese of anaboliese aktiwiteit nie, en kan bes beskryf word as 'n basaalverdowingsmiddel. Dit is reeds saam met stikstofsuboksied en suurstof in die verhouding van 3 : 1 gebruik. As 'n nie-barbituraat-preparaat hou dit interessante moontlikhede in. Die vernaamste punte wat die gebruik daarvan tot dusver aan die lig gebring het, is soos volg:

Na voorafgaande behandeling het atropien en petidien is 1-1.5 g. Viadril in ongeveer 'n 5-minuut-periode toegedien teen 'n finale konsentrasie van 1-1½%. Die inspuiting moet liefs in die middelonderarmaar geskied. Teen die einde van die inspuiting is die pasiënt gewoonlik aan die slaap. Hoe dit ook al sy, die maksimum-anestetiese effek, soos gemeet aan die refleks-aktiwiteit van die strottehoofspierstelsel, word nie onmiddellik opgemerk nie, maar ongeveer 10-20 minute later. Ná hierdie tyd is strottehoofsintubasie in die meeste gevalle moontlik sonder die gebruik van 'n kortwerkende spierontspanningsmiddel soos suksinielcholien. Strottehoofskramp is nie opgemerk nie. 'n Strottehoofsrefleks kan teenwoordig wees, maar die bande gaan oop na stimulasie. Een van die vernaamste eienskappe van Viadril is derhalwe skynbaar sy vermoë om spierrefleks-aktiwiteit te verminder.

Wanneer die strottehoofslugweg tot stand gebring is, kry die pasiënt stikstofsuboksied en suurstof. Onder die chirurgiese operasies wat reeds met behulp van hierdie tegniek uitgevoer is, kan melding gemaak word van skedel-, ortopediese, derm-, perineum-, borsen skildklier-prosedures. In tiroïedektomies is die pasiënte nie geïntubateer nie. Strottehoofskramp is egter nie tydens tiroïed-manipulasie opgemerk nie.

Aanvullende hoeveelhede Viadril is gewoonlik nie nodig nie. Selfs in die geval van prosedures wat tot 8 uur lank geduur het, was dit nie nodig om meer te gebruik nie. 'n bolic activity and is most properly described as a basal anaesthetic. It has been used in conjunction with nitrous oxide and oxygen in the ratio of 3 : 1. As a non-barbiturate preparation it holds out interesting possibilities. The main points so far established in its use are as follows:

After premedication with atropine and pethidine, 1-1.5 g. of Viadril are administered in about a 5-minute period in a final concentration of 1-1½%, the injections preferably being made into the median cubital vein. The patient is usually asleep by the end of the injection. However, the maximum anaesthetic effect, as measured by the reflex activity of the laryngeal musculature, is seen not immediately but some 10-20 minutes later. After this time laryngeal intubation is possible in most cases without the use of a short-acting muscle relaxant such as succinylcholine. Laryngospasm has not been seen. A laryngeal reflex may be present, but the cords open following stimulation One of the principal properties of Viadril therefore seems to be its ability to reduce muscle reflex activity.

When the laryngeal airway has been established, the patient is placed on nitrous oxide and oxygen. With this technique surgical operations performed include *inter alia* cranial, orthopaedic, bowel, perineal, breast and thyroid procedures. In thyroidectomies the patients were not intubated. However, laryngospasm was not seen during thyroid manipulation.

Supplementary amounts of Viadril are not usually required, it having been found unnecessary even for procedures lasting up to 8 hours. Coughing on the endotracheal tube (one of the early signs of lightening of the patient from the effects of Viadril) can be suppressed satisfactorily by small amounts of intravenous pethidine (15 mg.). Significantly smaller amounts of pethidine are required for Viadril anaesthesia than for thiopentone.

The blunting of reflex activity is further evidenced by abdominal muscular relaxation and absence of deep reflexes. With Viadril minimal or no muscle relaxants were required for abdominal surgery in the overseas clinical trials. The apparent ease with which the patient's respiration may be taken over is another interesting aspect of Viadril anaesthesia.

In the doses used thus far analgesia is not a prominent feature when Viadril is the sole agent. This inadequacy is compensated for by comparatively small amounts of pethidine and nitrous oxide in the 3 : 1 ratio already men-

3. Laubach, G. D., P'an, S. Y. en Rudel, H. (1955): Brit. Med. J., **2**, 254.

Gehoes in die endotracheale pyp (een van die eerste tekens dat die pasiënt van die effek van Viadril begin herstel) kan op 'n bevredigende manier onderdruk word met behulp van klein hoeveelhede petidien (15 mg.) binne-aars toegedien. Die hoeveelheid petidien wat nodig is met Viadril-narkose is opvallend kleiner as in die geval van tiopentoon.

Die verstomping van refleksaktiwiteit word verder bewys deur die verslapping van die buikspiere en die afwesigheid van diep reflekse. Oorsese kliniese proefnemings het bewys dat as Viadril vir buikchirurgie gebruik word, min of geen spierontspanningsmiddels nodig is nie. Die skynbare gemak waarmee die pasiënt se asemhaling oorgeneem kan word, is 'n verdere interessante aspek van Viadril-narkose.

In die dosisse wat tot dusver gebruik is, was analgesie nie 'n belangrike kenmerk as Viadril die enigste agens was nie. Die betreklik klein hoeveelhede petidien en stikstofsuboksied in die verhouding van 3 : 1 wat reeds genoem is, vergoed egter vir hierdie ondoelmatigheid. Oksigenasie van die pasiënte was heeltemal bevredigend met 25% suurstof, maar daar is aanduidings dat die minuutvolume-asemhaling effens verminder kan word. Die asemhalingstempo ondergaan in die reël nie betekenisvolle veranderings nie, maar daar is bewyse dat die volume getylug verminder word.

Sekere pasiënte met 'n onvaste bloeddruk kan 'n bloeddrukdaling toon as Viadril toegedien word. Dit is gewoonlik nie ernstig nie, en kan met behulp van metoksamien herstel word.

As die stikstofsuboksied weerhou word 1½-2 uur na die toediening van Viadril sal die pasiënt op pynlike prikkels reageer. Hy sal wurg, hoes en kan selfs skerp mondelinge bevele gehoorsaam. Met 'n dergelike dosis na ongeveer 5 uur op stikstofsuboksied, is die mate van herstel ietwat groter, want die pasiënt kan bes moontlik in staat wees om woorde te uit. As 'n chirurgiese prosedure laat in die oggend of vroeg in die middag voltooi word, is die pasiënt gewoonlik in staat om die aandmaaltyd te nuttig. Daar was minimale ná-narkose-mislikheid en braking.

Drie pasiënte (iedereen van wie aan 'n vaatongesteldheid gely het) het veneuse prikkeling ná die toediening van Viadril getoon. In al drie gevalle is die verdowingsmiddel toegedien in 'n klein aar aan die rugkant van die hand of die voet. Daar is derhalwe aanbeveel dat die finale konsentrasie van die verdowingsmiddel binne die bestek 1-1½% moet val, en dat dit tioned. Oxygenation of the patients has been quite satisfactory with 25% oxygen, but there is an indication that the minute volume of respiration may be slightly decreased. The respiratory rate is usually not significantly changed but there is some evidence that the tidal volume is decreased.

Certain patients with a labile blood pressure may show a fall in blood pressure when given Viadril. This is generally not profound and can be adjusted with methoxamine.

If the nitrous oxide is withdrawn 1½-2 hours after the administration of the Viadril, the patient will react to painful stimuli, gag, cough and may even respond to sharp verbal commands. On a similar dosage after about 5 hours on nitrous oxide, the degree of recovery is somewhat greater in that the patient may even be able to verbalize. If a surgical procedure is finished in the late morning or the early afternoon, the patient usually eats the evening meal. There has been a minimum of post-anaesthetic nausea and vomiting.

Three patients (each of whom had a vascular disorder) have shown venous irritation following the administration of Viadril. In each case the drug was administered in a small vein either on the dorsum of the hand or the foot. It has therefore been recommended that the final concentration of the drug be in the range of 1-1½% and that it be given into a large venous channel, such as the median cubital vein, where the flow is adequate. The problem of venous irritation is the subject of further investigation.

The effects of doses of Viadril smaller and larger than 1-1.5 g. are now being studied, as also its combinations with other anaesthetic agents.

Viadril is undergoing comprehensive tests in South Africa under the direction of Prof. W. E. Underwood of the Department of Surgery, University of Witwatersrand, in association with Dr. J. C. Nicholson of the Department of Anaesthetics of the Johannesburg Hospital. The steroid is first being studied on laboratory animals and thereafter a clinical evaluation will be carried out. Preliminary results[4] already indicate that this steroid can with advantage be given more slowly than has been reported so far and in an even greater dilution, e.g. 0.5%. These are important findings as they have a direct bearing on problems of pain along the course

4. Underwood, W. E. (1955): Personal communication.

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toegedien moet word in 'n groot aarkanaal, soos die middelonderarmaar waar die toestroming voldoende is. Die probleem van veneuse prikkeling word verder ondersoek.

Die effek van dosisse Viadril wat kleiner en groter as 1-1.5 g. is, word tans bestudeer, asook die kombinasie daarvan met ander verdowingsmiddels.

Viadril word tans in Suid-Afrika aan omvattende toetse onderwerp onder die leiding van prof. W. E. Underwood, van die Departement van Chirurgie, Universiteit van die Witwatersrand, in medewerking met dr. J. C. Nicholson van die Anestetiese Departement van die Johannesburgse Hospitaal. Die effek van die steroïed op laboratoriumdiere word eers bestudeer, en daarna sal 'n kliniese berekening gedoen word. Die voorlopige resultate[4] het reeds aangedui dat hierdie steroïed met voordeel stadiger toegedien kan word as wat tot dusver gemeen is, en in 'n selfs meer verdunde vorm, bv. 0.5%. Dit is belangrike bevindings, want hulle het 'n regstreekse uitwerking op die probleme van pyn in die loop van die ontvangende aar, sowel as op die moontlikhede van tromboflebitis.

Suid-Afrikaanse praktisyns sien met belangstelling vooruit na vollediger berigte oor hierdie steroïed-verdowingsmiddel, want dit lyk asof dit behoort aan 'n heeltemal nuwerwetse groep verdowingsmiddels, en dat dit die belofte van nuwe veiligheidsfaktore vir die chirurgiese praktyk inhou.

4. Underwood, W. E. (1955): Persoonlike mededeling.

KOLLEGE VAN INTERNISTE EN CHIRURGE VAN SUID-AFRIKA

Mediese praktisyns sal met belangstelling verneem dat die eerste vergadering van die voorlopige Komitee* van hierdie Kollege in Augustus 1955 plaasgevind het.

Gedurende 'n tydperk van 180 dae, gereken vanaf 21 Julie vandeesjaar, sal Geassosieerde Stigters nou tot die Kollege toegelaat word.

Toelating tot die Kollege sal hulle geregtig maak:

1. Om te nomineer;
2. Om vir Raadslede te stem;

* Die Komitee bestaan uit drs. B. W. Crowhurst Archer, M. Cole-Rous, J. S. Coller, S. Goldberg, A. J. Helfet, S. C. Heymann, W. Kark, J. A. S. Marr, T. B. McMurray, W. R. Phillips, M. Shapiro, A. W. Sichel, T. Schneider, A. G. Sweetapple, R. Theron, A. H. Tonkin en P. F. H. Wagner.

of the recipient vein as well as the possibilities of thrombophlebitis.

Fuller reports on this steroid anaesthetic will be awaited by South African practitioners with great interest as it appears to belong to an entirely novel category of anaesthetic agents with a promise of introducing new factors of safety into the practice of surgery.

THE COLLEGE OF PHYSICIANS AND SURGEONS OF SOUTH AFRICA

Medical practitioners will be interested to learn that the first meeting of the Steering Committee* of this College was held during August 1955.

For a period of 180 days from 21 July this year, Associate Founders can now be admitted to the College.

Admission to the College will entitle them:

1. To nominate;
2. To vote for the Council;
3. To have all the rights and privileges of Fellows except that they will have no letters after their names.

Office bearers of the Executive Committee elected recently are: Dr. A. W. Sichel (Chairman); Mr. M. Cole-Rous (Vice-Chairman) and Mr. A. Helfet (Librarian and Archivist). Mr. T. B. McMurray was elected Honorary Secretary, Treasurer and Public Officer. Those interested in taking advantage of this opportunity to become Associate Founders are invited to communicate with Mr. McMurray at P.O. Box 120, Cape Town.

* The Steering Committee consists of Drs. B. W. Crowhurst Archer, M. Cole-Rous, J. S. Coller, S. Goldberg, A. J. Helfet, S. C. Heymann, W. Kark, J. A. S. Marr, T. B. McMurray, W. R. Phillips, M. Shapiro, A. W. Sichel, T. Schneider, A. G. Sweetapple, R. Theron, A. H. Tonkin and P. F. H. Wagner.

* * * *

(*From* Dr. Fuller Albright's Famous Introduction to the Section on *Diseases of the Ductless Glands* in Cecil and Loeb's *Textbook of Medicine*, 8th ed.

'The author will not write the conventional introduction. He will not give the Greek derivation for the word "hormone", coined by Starling; he will not discuss the experiments of Claude Bernard which led to the concept of an internal secretion; he will not delve into the earliest beginnings of endocrinology which had as their *raisons d'etre* such ends as the procurement of manpower for the harem, the salvaging of a male soprano voice for the choir, the increased palatability that a rooster attains when he turns into a capon, and so on. He will not trace experimental endocrinology from 1849, when Berthold studied the effect of the gonads on the secondary sex characteristics of fowl, for the next hundred years down to 1949, when attention was

3. Op al die regte en voorregte van Genote, behalwe dat hulle geen letters agter hul naam sal hê nie.

Die volgende is onlangs tot ampsdraers van die Uitvoerende Komitee verkies: dr. A. W. Sichel (voorsitter); mnr. M. Cole-Rous (ondervoorsitter) en mnr. A. Helfet (bibliotekaris en argivaris). Mnr. T. B. McMurray is tot eresekretaris, tesourier en openbare amptenaar verkies. Diegene wat die geleentheid te baat wil neem om Geassosieerde Stigters te word, word uitgenooi om in verbinding te tree met mnr. McMurray, Posbus 120, Kaapstad.

focused on cortisone and its pituitary stimulator, adrenocorticotropic hormone (ACTH). But why mention such prosaic facts in 1950 when we are well into the schizo-atomic era and rapidly approaching, the author fears, the posthistoric era? It would be more in keeping to mention that a pellet of stilbestrol can now replace pregnancy as a promoter of lactation in cows. No, the author will not even list the names of describers of various endocrine syndromes—Addison with Addison's disease in 1855 down to, shall we say, the almost simultaneous elucidation of hyperparathyroidism in 1926 by Mandl and Du Bois.

Instead, he will discuss what endocrinology is, with special emphasis on what endocrinology is not, and then will comment on certain other aspects of the subject.'

INFORMATION FOR PHYSICIANS ON THE SALK POLIOMYELITIS VACCINE

Edited by

HART E. VAN RIPER, M.D.,

Medical Director, National Foundation for Infantile Paralysis, New York

PART I

ASSEMBLY OF RECENTLY PUBLISHED INFORMATION

The Salk Vaccine—Leonard A. Scheele, M.D.
The Public Health Service Technical Report on Salk Poliomyelitis Vaccine—June, 1955.
A.M.A. Statement on Poliomyelitis Vaccine—Walter B. Martin, M.D.
Evaluation of 1954 Field Trial of Poliomyelitis Vaccine: Summary Report—Thomas Francis Jr., M.D., and Staff.
Vaccine Administration to Allergic Patients—Sheppard Siegal, M.D.
Vaccination Against Paralytic Poliomyelitis: Performance and Prospects—Jonas E. Salk, M.D.
Salk Bibliography.
Poliomyelitis Vaccination—Alexander D. Langmuir, M.D.
A Perspective on Poliomyelitis Prevention—Editorial from the *American Journal of Public Health.*

PART II

ANSWERS TO QUESTIONS CONCERNING

Dosage and schedule adminstration.
Who should get vaccine.
Vaccination during pregnancy.
Contra-indications.
Minimal reactions to vaccine.
Factors affecting immunity.
Problems of vaccine manufacture and storage.
Research problems.

PART I

This publication has two basic purposes: (1) to assemble for physicians some of the important material on the Salk vaccine that has appeared in the professional literature since the vaccine was evaluated, and (2) to answer clinical questions about the vaccine that physicians and their patients are currently asking.

Included in this assemblage of material are two exceptionally significant documents—the Francis report of April 12, 1955, presented here in abstract; and the U.S. Public Health Service Technical Report on Salk Poliomyelitis Vaccine, issued June 10, 1955, of which extracts are given here. The position of the American Medical Association on the use of the vaccine is presented in a statement by Dr. Walter B. Martin, immediate past-president of the American Medical Association. These original documents should serve to orient physicians on important aspects of the Salk vaccine.

The second part of this publication is made up of answers to questions from the medical profession about the vaccine and its use. A perusal of these questions and answers will bring the physician up to date on the use of the Salk vaccine in 1955—and later.

The availability of vaccine for clinical use by physicians depends upon the six manufacturers of the vaccine and the U.S. Public Health Service, which is legally responsible for licensing it and controlling its standards of safety and potency. The role of the National Foundation in the distribution of vaccine is limited, as it has always been, to

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the supplying of state health departments with sufficient vaccine to complete a schedule of inoculations for children in the first and second grades in school. The details of these programs are being worked out individually in each state and community.

In general summary of what will become apparent upon more complete reading of this assembly of information for physicians on the Salk poliomyelitis vaccine, the following statements may be made:

1. As properly manufactured under revised standards, the Salk vaccine is safe and effective. It should reduce the risk of paralytic poliomyelitis by 80% to 90% among the children who receive it.

2. The vaccine is still in short supply and as long as it remains so certain priorities for its administration should be observed. The suggested categories of priority are as follows: (1) 5 to 9 age group; (2) under 5 years; (3) 10 to 14 years; (4) 15 to 19 years; and (5) pregnant women.

3. The recommended dosage schedule is 1 c.c., intramuscularly, repeated in 2 to 4 weeks and again (booster shot) after 7 months. The vaccination programme may be undertaken at any time—even during a polio epidemic.

4. Research on the Salk vaccine and polio vaccines in general is continuing. Important projects are to find a substitute for the Type I strain now used in the vaccine and to determine the duration of immunity following primary vaccination and the booster shot(s).

THE SALK VACCINE

The development and successful trial of the Salk vaccine against paralytic poliomyelitis is a major step toward control of a crippling disease. It represents the culmination of a truly historic medical and public health achievement.

This development of a successful vaccine places a great responsibility on the physicians, the public health agencies and the parents in our nation. I am confident that physicians and health officials will conscientiously conserve and put to best use the supply of vaccine. Parents should co-operate with them. As the supply increases, there will be enough for all who wish to be immunized.

Within our time, therefore, we can expect to see effective control of crippling polio. I offer my sincere congratulations to all who have contributed to this great effort to protect future generations from the specter of poliomyelitis.

—Leonard A. Scheele, *Surgeon-General*, U.S. Public Health Service, April 12, 1955.

From the U.S. Department of Health, Education and Welfare

THE PUBLIC HEALTH SERVICE TECHNICAL REPORT

on

SALK POLIOMYELITIS VACCINE

June 1955

I. Letter of transmittal from Leonard A. Scheele, M.D., to Mrs. Oveta Culp Hobby.
II. Summary of the Public Health Service Technical Report.
III. Epidemiological Experience, April-May 1955—Extracts from Chapter 11, Part III, of the Public Health Service Technical Report.
IV. Amendment No. 2, May 26, 1955, to the Minimum Requirements for Poliomyelitis Vaccine—Extracts of key points in revised requirements and tabular summary of amendments to Minimum Requirements.

I: LETTER OF TRANSMITTAL FROM LEONARD A. SCHEELE, M.D., TO MRS. OVETA CULP HOBBY

DEPARTMENT OF HEALTH, EDUCATION AND WELFARE
PUBLIC HEALTH SERVICE
WASHINGTON 25, D.C.

June 10, 1955

Dear Mrs. Hobby: I am pleased to transmit herewith a technical report on the status of the Salk poliomyelitis vaccine.

The April 12 announcement that a vaccine for the prevention of paralytic poliomyelitis had been successfully developed and tested brought hope to millions of American families that poliomyelitis could at last be conquered. Events which in the traditional course of scientific development would have covered years were telescoped into months and, as a result, both successes and failures have been magnified. In the long run, however, the Nation and the world will surely have gained from efforts to speed the availability of an effective immunizing agent against this disease.

On the other hand, difficulties arose which called for systematic review of the production and testing processes, and the adoption of more rigid safety requirements. This has resulted in a delay in the vaccination program which had been planned on a Nation-wide basis.

A complete review of the subject is warranted because the events of the past month have occurred with such speed and frequency that it has been impossible to present a cohesive account, from day to day, of this complex problem. The widespread professional and public interest in the vaccine also warrants a review to achieve thorough understanding. This technical report attempts to provide such a review. It records the events and experiences on

which the actions of the Public Health Service have been based, and it outlines plans for the future with respect to poliomyelitis vaccine as one of the biologic products for which the Public Health Service has certain responsibilities.

Our most fundamental objective is to promote the health and safety of the American people. We are therefore concerned with an effective vaccine for the prevention of poliomyelitis, and we are concerned with a safe vaccine. As in all scientific and medical endeavor, we must weigh potential benefits against possible hazards. This we have done in dealing with the Salk poliomyelitis vaccine.

We have every belief that this vaccine will fulfill its bright promise as a major advance in the prevention and control of a disease that has shadowed the lives of children and young adults for many generations.

Respectfully,
s/s Leonard A. Scheele,
Surgeon-General.

The Secretary,
Department of Health, Education and Welfare,
Washington 25, D.C.

II: SUMMARY OF THE PUBLIC HEALTH SERVICE TECHNICAL REPORT

This report presents the technical problems involved in the production, testing and safety of Salk poliomyelitis vaccine. It also describes the responsibilities of the Public Health Service in control of the manufacture of the vaccine as a biologic product.

The vaccine as prepared for the 1954 field trial was an experimental product made by commercial producers for the National Foundation for Infantile Paralysis. After some initial difficulty, the industrial firms were able to turn out a good product, and the field trial was carried out successfully. Vaccine production for the field trial permitted the laboratories of industry and the Public Health Service to acquire experience in testing.

As a result of its studies over a period of two years, which included participation with industry and with Dr. Salk in testing of vaccine for the field trial, the Public Health Service planned to act quickly on licensing if the analysis of the field trial data showed that the vaccine was safe and effective. It had issued prospective Minimum Requirements in May 1954, as advisory for pharmaceutical laboratories which might wish to manufacture and store vaccine intended for commercial use pending decision to license the product. When the success of the field trial was reported on 12 April 1955, official Minimum Requirements were issued, and six manufacturers, each of which had produced vaccine under the provisional requirements, were granted licenses.*

Records and samples of lots of vaccine had been submitted to the Public Health Service Laboratory of Biologics Control prior to April 12, and within the next few days, those which were considered acceptable were released. Most biologic products for commercial distribution are released on the basis of an examination of the detailed record of events in manufacture and testing (known as a protocol), with or without further testing by the Laboratory of Biologics Control. Release of most of the lots of poliomyelitis vaccine was based on review of the manufacturing protocols. Tissue culture tests for the presence of live virus were completed prior to release by the Laboratory of Biologics Control on about half of these lots and monkey tests were completed on six lots involving at least one lot from each of five manufacturers.

On April 26, six cases of poliomyelitis were reported among children who had received vaccine manufactured by the Cutter Laboratories. At the request of the Public Health Service, this firm immediately recalled all of its vaccine. The investigation of the Cutter Laboratories which ensued was later extended to the entire industry and led to a temporary suspension of the Nation-wide vaccination program.

The Public Health Service on April 28 established a Poliomyelitis Surveillance Unit within its Communicable Disease Center in Atlanta, Georgia. This Unit is investigating all reported cases of poliomyelitis, whether or not associated with vaccine. Sixteen virus laboratories, throughout the nation, are cooperating in examining and reporting upon specimens collected from cases and suspected cases. The epidemiological data so far obtained clearly define the Cutter incident as an outbreak with characteristics of a common source epidemic. The cases of poliomyelitis following use of vaccines made by the other

**Editor's Note*: The following individuals met with members of the Staff of the National Institutes of Health in Ann Arbor on 12 April 1955, and advised the Surgeon-General of the Public Health Service that he recommend licensing of poliomyelitis vaccine (Salk) to the Secretary of Health, Education and Welfare: William McD. Hammon, John R. Paul, M.D., Albert B. Sabin, M.D., Howard J. Shaughnessy, Ph.D., Joseph E. Smadel, M.D., and Thomas B. Turner, M.D. The following staff members of the National Institutes of Health were present at the meeting: Joseph Bell, M.D., Victor Haas, M.D., Karl Habel, M.D., Roderick Murray, M.D., and William Workman, M.D. This information was revealed at a Congressional hearing.

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manufacturers have not been more numerous than would be expected at this season except for a few cases which suggested (but were too few to be conclusive) an association with one lot of vaccine produced by Wyeth. That firm has withdrawn the unused portion of this lot.

The Salk vaccine is a suspension of poliomyelitis virus inactivated by formaldehyde to render the virus harmless but still capable of inducing the production of antibodies. The vaccine contains inactivated virus of each of the three types. The original concept of vaccine preparation was that the process itself assured a wide margin of safety. Safety tests for the vaccine were conceived to detect both mass contamination resulting from accidents in manufacture, and residual live virus which the process was intended to eliminate.

The intensive investigations of the past 5 weeks indicate that the records which manufacturers were required to submit did not include certain data which are essential for an adequate assessment of consistency in performance. The protocols submitted related only to lots of vaccine proposed for clearance, and gave no information concerning lots discarded in the course of manufacture. Further, the information requested did not bring out certain data on processing and testing now known to be important.

The total experience of the manufacturers now reveals that the process of inactivation did not always follow the predicted course, since positive tissue culture tests not infrequently occurred after the expected completion of the inactivation process. Greater dependence, therefore, must be placed on sensitive tests for very small quantities of residual live virus as part of process control than would otherwise be the case.

Two types of test are used to determine the presence or absence of live virus in the vaccine: the monkey test and the tissue culture test. The tissue culture test has been found to be more sensitive than the monkey test. It must be performed with a large enough sample of vaccine and under closely controlled conditions if it is to have maximum value. The theoretical considerations which govern inactivation and testing have been analyzed in the light of information developed during this inquiry.

As a result of the inquiry and of analysis of the manufacturers' experience and records, changes were made in processing control and safety testing. Revised requirements in the testing procedures were established, and the release of vaccine was resumed. The modifications provide greater assurance of safety. As a result of the review and the institution of revised requirements, the production and availability of vaccine has been delayed.

The Salk vaccine applies new practices in the production of viral vaccines. The vaccine has progressed from the experimental level to large-scale production with unprecedented rapidity. This speed, reflecting the increased tempo of all medical research, created problems in biologics control amenable to solution only with the accumulation of knowledge and experience. It is likely that other problems of equal complexity will be raised by the development of other new viral vaccines. Action taken by the Public Health Service to deal with both the current and the long-range problems include:

1. Amendment of Minimum Requirements for the production and testing of poliomyelitis vaccine.
2. Incorporation of Minimum Requirements in official regulations as mandatory standards.
3. Creation of a Technical Committee on Poliomyelitis Vaccine.
4. Creation of a Division of Biologics Standards, with strengthened staff and facilities.
5. Increased on-site plant surveillance and consultation.
6. Reoriented testing and research program.
7. Establishment of a Poliomyelitis Surveillance Unit.
8. Review of legislative authority.

III: EPIDEMIOLOGICAL EXPERIENCE, APRIL-MAY 1955—EXTRACTS FROM CHAPTER 11, PART III, OF THE PUBLIC HEALTH SERVICE TECHNICAL REPORT

POLIOMYELITIS ASSOCIATED WITH VACCINATION

A total of 113 poliomyelitis cases, with 5 deaths, were recognized among nearly five and one-half million individuals within one month after injection of poliomyelitis vaccine (Table I). The greatest number of cases associated with the product of any one manufacturer was 69, of which 59 were paralytic. This occurred among approximately 409,000 recipients of vaccine prepared by the Cutter Laboratories. The attack rate in this group was 17 per 100,000 in 1 month.

Most of these cases were reported from California and Idaho, where the National Foundation for Infantile Paralysis provided Cutter vaccine for school clinics, but a scattering of cases occurred in other parts of the country where the vaccine had been released in small quantities through commercial channels. Cutter vaccine was used for

school clinics in Arizona and New Mexico; but no cases have been reported among vaccinated children from these States.

Among approximately 4,985,000 people who received the products of four other manufacturers, a total of 44 cases was reported, only 19 of which were paralytic. The attack rate in this group was less than 1 per 100,000 in 1 month.

RESULTS OF EPIDEMIOLOGICAL SURVEY

A total of 113 poliomyelitis cases (78 paralytic and 35 non-paralytic) had developed by May 21 among more than 5 million individuals vaccinated against poliomyelitis since April 14, 1955. Comparison of reported and expected numbers of cases indicates association between Cutter poliomyelitis vaccine and an increased incidence of poliomyelitis. The distribution of Cutter-associated cases by interval between inoculation and date of paralysis, and the correlation between sites of inoculation and paralysis are strikingly similar to experimental data. These findings indicate that at least some of the Cutter-associated cases developed from the use of poliomyelitis vaccine containing infective virus[1] [Table II].

Evidence is not conclusive but suggests there may have been a similar association with a few cases following the use of Wyeth vaccine. In contrast, the data indicate that the incidence of poliomyelitis after use of the products of other manufacturers was probably coincidental.

[1] Additional data relating cases to specific lots of vaccine are under analysis in connection with the study of the Cutter plant processes, and will be included in a report to be made when all phases of this study are completed.

TABLE I: POLIOMYELITIS CASES AND ATTACK RATES IN RECIPIENTS OF POLIOMYELITIS VACCINE, WITH ONSETS BETWEEN APRIL 20 AND MAY 21, 1955.

Vaccine Manufacturer	*Approximate Number of Vaccines (total)*	*Cases*			*Total Attack Rates per 100,000 per month*[1]
		Paralytic	*Non-paralytic*	*Total*	
Total	5,394,000	78	35	113	2
Cutter	409,000	59	10	69	17
Lilly	2,514,000	10	19	29	1
Parke, Davis	1,234,000	2	0	2	1
Pitman-Moore	461,000	0	2	2	1
Wyeth	776,000	7	4	11	1

1. These attack rates are of limited significance in themselves, since vaccines of some manufacturers were used in areas in which the seasonal rise in incidence already had begun.

TABLE II: COMPARISON OF REPORTED AND EXPECTED NUMBERS OF POLIOMYELITIS CASES IN CHILDREN RECEIVING POLIOMYELITIS VACCINE IN NFIP CLINICS FROM APRIL 15 TO MAY 7, 1955

Vaccine Manufacturer	*Approximate Number of Vaccines (NFIP Clinics only)*	*Poliomyelitis Cases—with Onset from April 20 to May 21*	
		Reported Number[1]	*Expected Number*[2]
Total	4,844,000	79	36
Cutter	309,000	35	5
Lilly	2,514,000	29	24
Parke, Davis	834,000	2	3
Pitman-Moore	411,000	2	2
Wyeth	776,000	11	2

1. Reported cases aged 6-8 years with onset between April 20 and May 21. Includes both paralytic and non-paralytic cases since expected numbers for comparison are based on crude rates which include all cases reported as poliomyelitis in previous years.
2. Expected cases if the estimated, age-adjusted, median attack rate for the previous 5 years had pertained in the vaccinees of 1955.
These rates are specific for geographic areas where the various poliomyelitis vaccines were used.

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IV: AMENDMENT NO. 2, MAY 26, 1955, TO THE MINIMUM REQUIREMENTS FOR POLIOMYELITIS VACCINE—EXTRACTS OF KEY POINTS IN REVISED REQUIREMENTS AND TABULAR SUMMARY OF AMENDMENTS TO MINIMUM REQUIREMENTS

The Minimum Requirements: Poliomyelitis Vaccine, 1st Revision dated April 12, 1955, are hereby amended, effective this date, as follows:

3.2 *Single Strain Vaccine Tissue Culture Tests.*—During inactivation each monovalent bulk strain pool is tested for infectious virus by tissue culture methods before pooling to make the final poliomyelitis vaccine. Two tests are made, separated by an interval of at least three days during inactivation at 37° C.

The sample for each test consists of at least 500 ml. The sample is inoculated into five or more tissue culture bottles of a suitable capacity, the ratio of the vaccine to the nutrient fluid being approximately 1:1 to 1:3, and the area of the surface growth of cells being approximately 3 sq. cm. per ml. of vaccine. The tissue culture bottles are observed for at least 14 days.

A first subculture is made by planting at least 2% of the volume from each original bottle into suitable tissue culture containers at the end of seven days followed by refeeding.

A second subculture is made from each original bottle in the same manner at the end of 14 days.

The first and second subcultures are each observed for at least seven days.

If cytopathogenic effect occurs at any time, or if cellular degeneration appears before the 7th day or before degeneration occurs in uninoculated control cultures, the pool is considered infectious if active poliomyelitis virus can be identified, and the pool is not acceptable for the preparation of the final vaccine.

3.3 *Final Vaccine Tissue Culture Test.*—Each lot of final vaccine is prepared by pooling approximately equal parts of monovalent bulk strain pools which have passed all tests described in section 3.2.

A sample consisting of at least 1,500 ml. of the final vaccine is tested by tissue culture methods and its acceptability determined as described in section 3.2.

Furthermore, a lot which has yielded a positive tissue culture test in the final pool is not acceptable for release unless it passes two consecutive negative tissue culture tests with separate samples of at least 1,500 ml. each. The final pool may not be reheated.

TABULAR SUMMARY OF AMENDMENTS TO MINIMUM REQUIREMENTS FOR POLIOMYELITIS VACCINE

ORIGINAL	REVISED
Single Strain Pool	
1. Test 1 milliliter per liter of material.	1. Test minimum of 500 cc's per pool.
2. Must have 1 negative test.	2. Must have 2 consecutive negative tests.
3. No restriction on reheating.	3. Can reheat only once; if this is done, it must be followed by two successive negative tests 3 days apart.
Trivalent Pool	
1. Test 1 milliliter per liter of material.	1. Test minimum of 1,500 cc's of material.
2. No specific restriction on number of times material can be reheated, although conventionally not done more than once.	2. Cannot be reheated.
3. Must have 1 negative test.	3. Must have 1 negative test.
Final Container	
1. Not tested for live virus.	1. Test random samples of filled bottles to determine if there has been accidental contamination by polio virus.

CRITERIA FOR RELEASE OF VACCINE ALREADY PRODUCED

Lots Produced But Not Yet Released

Vaccine in this category is being retested in larger volume to approximate as nearly as possible the tests for new material according to criteria established by Technical Committee on Poliomyelitis Vaccine.

Lots Already Released, Now Being Recleared

Vaccine in this category is recleared if epidemiological evidence demonstrates that it can be used with safety or if retested.

A.M.A. STATEMENT ON POLIOMYELITIS VACCINE*

WALTER B. MARTIN, M.D.

Walter B. Martin, M.D., immediate past-president of the American Medical Association, has publicly assured the co-operation of the medical profession in trying to work out any technical problems related to the use of poliomyelitis vaccine. In a statement released through A.M.A. headquarters, Dr. Martin said:

'The rechecking of manufacturing procedures and laboratory data following the outbreak of poliomyelitis in a few vaccinated children has caused unavoidable delay. In the midst of such tension the Eisenhower administration is to be commended for conducting a careful and scientific review of the entire situation before permitting continuance of the programme.

'In behalf of myself and the A.M.A. Board of Trustees, I have assured President Eisenhower that the nation's physicians will co-operate in limiting poliomyelitis vaccination to children from five through nine until the vaccine is available in larger supply. Children in this age group who do not receive the vaccine during the current programme of the National Foundation for Infantile Paralysis for first and second graders will be vaccinated after its completion.

'The American Medical Association is asking all physicians to administer vaccine only to children in the priority age group of five through nine until further notice. This will assure that the vaccine will be used first for those most susceptible to the disease.

'Physicians are all being asked to keep a record on each child vaccinated. This will include the name and age, the date of vaccination, the site, the manufacturer of the vaccine used and the lot number.

'This voluntary priority vaccination plan follows the recommendation of the National Advisory Committee on Poliomyelitis Vaccination approved by Secretary Oveta Culp Hobby and contained in her report to the President on May 16.'

* From the *Journal of the American Medical Association* 158:6, 483 (June 11) 1955.

An abstract of the 'Francis Report'

EVALUATION OF 1954 FIELD TRIAL OF POLIOMYELITIS VACCINE: SUMMARY REPORT*

THOMAS FRANCIS, JR., M.D., ROBERT F. KORNS, M.D., ROBERT B. VOIGHT, B.S., MORTON BOISEN, B.A., FAY M. HEMPHILL, PH.D., JOHN A. NAPIER, EVA TOLCHINSKY,

From the Poliomyelitis Vaccine Evaluation Centre, University of Michigan, Ann Arbor, Michigan,

April 12, 1955

The crux of this report is that the trivalent, formalinized vaccine developed by Dr. Jonas Salk has proved to be up to 80-90% effective in preventing paralytic poliomyelitis under natural conditions of exposure to the disease. The report both details and summarizes the results of the 1954 vaccine field trials undertaken by the National Foundation for Infantile Paralysis to test the effectiveness of the vaccine. The whole venture represents an unprecedented degree of public and professional co-operation in carrying out a massive medical experiment designed to answer a significant and pressing question.

The heart of the study undertaken at the independent Poliomyelitis Vaccine Evacuation Center at the University of Michigan was to evaluate the differences in incidence of poliomyelitis among children who received the vaccine and comparable control groups who did not. The period of observation of these

* Note: This report was reprinted as Part II of the *American Journal of Public Health* 45:5 (May) 1955.

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differences was the second half of the year 1954.

The mass of data accumulated in the study also permitted answers to many corollary questions. For example, the safety of the vaccine was powerfully confirmed; again, the ability of vaccination to protect household contacts against paralytic poliomyelitis was firmly demonstrated.

The report itself presents the outline of the plan of study of the 1954 field trials and analyzes the statistical data accumulated at the evaluation center. The statistical analyses reflect the fact that two types of studies were actually undertaken. One dealt with 'observed control' areas; the other with 'placebo control' areas. Observed control studies were carried out in 127 areas in 33 states; placebo control studies were done in 84 test areas in 11 states.

It turned out, in light of the fact that the locale of polio epidemics is notoriously difficult to predict, that an excellent selection of test areas was actually made. The incidence of poliomyelitis in the test areas was 26% higher than for the rest of the country, thus adding to the statistical significance of the study.

The vaccination phase of the field study was carried out in April, May and June of 1954. The study population in the placebo control areas included 749,236 children in the first, second and third grades of school. Of these, approximately 61% requested participation in the trials. Hence approximately 200,000 children received three injections of vaccine and about a like number three injections of placebo (which was Mixture 199, the synthetic medium used to grow polio virus in tissue culture). In the observed control areas, the study population totalled 1,080,680 children in the first three grades in school; of these, approximately 220,000 second grade children (20.5% of the total) received three doses of the vaccine.

The first problem in the evaluation proper was to collect and verify basic information on each of the 1,829,996 children in the study population. These data, in addition to name, address, age, sex and school, included a history of polio or other crippling disease, participation status and dates of inoculation, if any. This material was transferred to punch cards. Tables describing the study population were prepared to serve as denominators against which discovered cases of polio could be placed. This made it possible to determine polio attack rates in the vaccinated as against the control groups.

Great care was taken in selection of control groups. For example, an interview survey was conducted in 1,100 families in the study population to discover differences between those which requested participation of their children in the field trials and those who did not. This study demonstrated higher income level, greater health awareness and community participation among the families who wished their children included in the vaccine study; and helped specify the most useful control group to be used in the observed control areas.

Investigations of the safety of the vaccine were meticulously carried through. Minor reactions and so-called major reactions to the vaccination procedure were reported to the center. None of the major reactions could clearly be attributed to inoculation. Minor reactions included fainting, nausea, dizziness, slight rashes and colds. Major reactions included illnesses characterized by severe rashes, high fevers, severe pains in the arms or legs, any paralysis and major diseases of the nervous system or the kidneys.

In the placebo control areas there were 931 minor reactions reported in the vaccinated children and 939 in those who received placebo—an incidence of 0.4% for each group. The major reactions numbered 9 among the vaccinated children and 13 among those who received placebo. In the observed control areas, 1,694 minor reactions were observed—an incidence of 0.7%—and a total of 7 major reactions. Hence it appeared that the vaccine could not be implicated as a significant cause of untoward reactions.

Further assessment of the safety factor was made in follow-up studies of school absenteeism following inoculations in Pittsburgh and in Schenectady, N.Y. The experience was identical in vaccinated and control subjects. The reactions in vaccinated children failed to indicate any possible relationship to kidney disease, a point previously raised because the vaccine contains minute quantities of monkey kidney protein.

A special review was made of 129 cases of poliomyelitis occurring in the study population up to the first month after inoculation, the period during which any cases occurring might be considered to be related to the vaccine. Here again there was no evidence implicating the vaccine as a source of infection. Furthermore a study of the location of paralysis failed to demonstrate any localization of involvement

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to the left arm, where all injections were given.

INCIDENCE OF POLIO IN THE STUDY POPULATION

In the study population of 1,829,916 children, a total of 1,103 cases considered to be poliomyelitis was reported to the evaluation center between May 1 and December 31, 1954. Ninety of these cases, however, occurred between May 1 and two weeks after the third injection—that is during the vaccination period. They were therefore eliminated from the analysis.

The cases for analysis totalled 1,013, of which 428 were in the placebo areas and 585 in the observed control areas. The polio incidence rates were 54 and 57 cases per 100,000 study population, respectively.

Of the 1,013 reported and analyzed cases, about two-thirds (67.6%) were classified as paralytic poliomyelitis—minimal paralysis was included in this group. Of the remainder of the cases, 17.6% were recorded as non-paralytic polio and 14.5% as doubtful or non-polio.

MEASUREMENT OF ANTIGENIC POTENCY OF LOTS OF VACCINE

Blood samples were collected from 40,881 children in the study population before vaccination, two weeks after vaccination and again five months later. Laboratory reports on titration studies of the sera of 9,000 children were available for analysis. This material was used to classify lots of vaccine into categories of good, moderate, low moderate and poor. Certain lots of vaccine were used in combination with others. A grouping of lots and combinations was made in accordance with the titration response of the blood sera.

On this basis five lots and three combinations were called good; three lots and two combinations were poor. The others fell into intermediate positions. In general antigenic response to Type I virus was lower than to Type II and Type III, which tended to be more or less similar.

Some persistence of antibodies was detectable four to five months after the vaccination series was completed. However there was generally a decline in titer of about one dilution. The decline in antibody titer was especially marked in children who were vaccinated with so-called poor lots of vaccine. Nevertheless, the distribution of antibody levels in vaccinated children, five months after vaccination, persisted in being distinctly higher than among the control groups.

NATURE OF FOLLOW-UP INVESTIGATIONS

Whenever a case of actual or suspected poliomyelitis in the study population was reported to the evaluation center, a detailed follow-up investigation was set in motion. In addition to obtaining a detailed initial report, the center also received a clinical-epidemiological report, a muscle evaluation report (from specially instructed physical therapists who examined patients 10 to 20 and again 50 to 70 days after onset of illness), a review of these findings by clinical experts, and laboratory reports on blood and stool specimens collected from the patients.

The laboratory procedures included efforts to isolate poliomyelitis or other viruses from the specimens and a search for polio antibodies. Efforts were made to standardize procedures as far as possible so that all findings would be comparable. Rigid criteria were established for reaching a final diagnosis.

Minimal criteria for classifying a case as paralytic poliomyelitis included the following findings reported on physical therapists' examinations and reviewed by physicians: (1) spotty, asymmetrical involvement with a grade of good on either first or second muscle examination in muscles characteristically affected by poliomyelitis—deltoid, triceps, finger extensors, opponens pollicis, gluteus medius, quadriceps, gastrocnemius, anterior tibialis; (2) a grade of fair on any single muscle or muscle group; and (3) definite indications of facial, laryngeal or pharyngeal involvement alone, or of the palate with other evidence. This group was designated as Grade I spinal paralytic poliomyelitis. Bulbar involvement was considered independently of muscle score.

Cases with spinal and bulbar involvement could be classified into grades of spinal involvement with the accompanying bulbar severity designated. Five grades of severity of spinal paralytic poliomyelitis were established on the basis of muscle score indicating anatomical mass of involved muscles.

Laboratory studies of reported cases of poliomyelitis were undertaken on as comprehensive a scale as feasible; however, unsatisfactory specimens and failure to receive specimens reduced the total data.

A typed poliomyelitis virus was recovered from 426 patients; viruses not identified as poliomyelitis were recovered from 72. Of the poliomyelitis viruses reported isolated, 56%

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were Type I, 12% Type II, 32% Type III. Serologic studies—neutralization tests done in tissue culture — were complete in 367 instances. Interpretation of these data is complex and not clearcut. It can be accepted, however, that if the acute illness observed was poliomyelitis, the type of virus was serologically indicated by the levels of antibody in acute and convalescent sera.

The frequency with which virus was isolated tended to rise with the increasing clinical severity of illness. However, the failure to recover virus from a significant number of characteristically paralytic cases indicates that such failure is not sufficient at the present time to exclude the patient from the classification of poliomyelitis. In arriving at a final classification of poliomyelitis, a combination of clinical findings, muscle evaluation and laboratory data had to be used.

SUMMARY OF EVALUATION RESULTS

The 1,013 cases of poliomyelitis reported in the study population during the observation period were analyzed through a series of steps which were designed to establish diagnosis more firmly, step by step. In each of four steps the difference in the incidence of poliomyelitis among the vaccinated children and the unvaccinated children (control groups) was compared. The comparisons were made separately for the placebo areas and the observed control areas.

Through these four stages of "purification" of diagnosis, there was a progressive increase in the calculated effectiveness of the vaccine. In other words, the more certainly the diagnosis of poliomyelitis was confirmed (or disproved), the more evident it became that the vaccine was preventing paralytic poliomyelitis.

The crudest data subjected to analysis were the total cases reported. From this total were eliminated both the non-polio cases and the non-paralytic cases. Estimate of the effectiveness of the vaccine on non-paralytic cases was deemed to be statistically unreliable.

When paralytic cases only re-remained, the estimated effectiveness of the vaccine was 72% in the placebo areas and 62% in the observed control areas. A lower limit of effectiveness was also computed for all reported percentages of effectiveness by application of the binomial theory as a measure of statistical significance.

A second step in the refinement of data was to separate spinal paralytic cases from bulbar-spinal cases, which present a more definite clinical picture and yielded a higher percentage of virus recoveries. In placebo areas the vaccine was calculated to be 60% effective against spinal paralytic cases and up to 94% effective in preventing bulbo-spinal poliomyelitis, an extremely effective result. The estimates for the observed control areas were not so impressive.

A third step in analysis dealt with laboratory-confirmed spinal and bulbo-spinal cases. A higher degree of confidence in diagnosis could be placed here, since the mild paralytic cases, which might not have been related to the polio virus, were eliminated if not laboratory-confirmed.

In the placebo areas, the effectiveness of the vaccine against bulbo-spinal cases was again estimated at over 90% (91%); in the observed control areas it stood at about 60%. But in both placebo and observed control areas, the effectiveness of the vaccine as measured against spinal paralytic cases rose to 82% or 83%, respectively.

The fourth analytic step included cases from which a specifically identified type of polio virus was recovered. In this group, in placebo areas, the vaccine proved highly effective against Type II (100% effective) and Type III (92% effective) but somewhat less effective (68%) against Type I. This confirms the previous demonstration that most lots of vaccine were less antigenic for Type I than for the other two types.

Over-all an effectiveness of 80% against the three types of viruses was noted in the placebo areas; but this figure does not state the effectiveness of the best lots of vaccine. In the observed control areas the over-all effectiveness was noted at 69%.

Greater confidence generally has been placed in the results obtained from the placebo area studies, where strictly controlled and almost identical vaccinated and control groups were subjected to analysis. On this basis it may be suggested that the vaccine was 80% to 90% effective in preventing paralytic polio—60% to 70% against the disease caused by Type I virus and 90% or more effective against the disease owing to Type II and Type III virus. There is no single figure to sum up the total vaccination experience.

COROLLARY STUDIES IN EVALUATION REPORT

1. The vaccine apparently protected children against paralytic polio from family contacts. In the placebo control area only 1 vaccinated child residing in a household where an index case of poliomyelitis was reported was stricken

with the disease. On the other hand 8 placebo-inoculated cases developed laboratory-confirmed cases. A total of 477 households were investigated, divided almost equally between the vaccinated group and the placebo group.

2. Refined analysis of the field trials carried out in Finland and Canada during 1954 revealed that the vaccine had a significant preventive effect and confirmed, with much smaller numbers, the American experience.

3. When measured against the prevention of residual paralysis, as reported on second muscle examinations, the vaccine appeared to have a striking preventive effect.

4. Within the narrow age-band limits of the evaluation study, the vaccine appeared to increase in effectiveness as age increased.

5. Based on experience in Massachusetts and central New York state, where extremely mild cases were reported, leaving doubt that the illnesses were poliomyelitis at all, more study of the role of 'orphan' viruses in causing illness is indicated.

6. The use of gamma globulin in field trial areas during the summer of 1954 was equally distributed between vaccinated and non-vaccinated children and did not interfere with a proper evaluation of the vaccine.

VACCINE ADMINISTRATION TO ALLERGIC PATIENTS*

Because the virus used in the Salk vaccine is cultured on monkey kidneys and 200 units of penicillin are added to each milliliter of culture medium, some question has been raised concerning administration of the vaccine to allergic children. The present report clarifies these points, as follows:

SUMMARY AND CONCLUSIONS

1. Sixteen adult patients with allergic rhinitis and asthma due to multiple pollen, inhalant and food sensitivity, and with strongly positive skin test reactions to animal danders, were tested with poliomyelitis vaccine. Intracutaneous tests and trial subcutaneous injections of the undiluted vaccine did not demonstrate evidence of cross-sensitivity.

2. Intracutaneous and trial subcutaneous tests with poliomyelitis vaccine in a patient with persistent penicillin sensitivity did not elicit any reaction attributable to its possible penicillin content. Tests in passive transfer sites with the serum of a patient anaphylactically sensitive to penicillin and known to contain a high titer of reagents were also negative, indicating the penicillin content of poliomyelitis vaccine is negligible.

The vaccine should offer no hazard either to persons allergic to penicillin or as a source of newly acquired penicillin sensitization.

3. Among 63 consecutive control adult subjects, intracutaneous tests with poliomyelitis vaccine showed negative immediate reactions. Of 58 adults only three showed a definite, although slight positive delayed, 24-hour skin reaction, to 0.1 ml. of the vaccine.

* Siegal, S., The Penicillin Content of Poliomyelitis Vaccine (Salk) and its Administration to Allergic Patients, *American Journal of Public Health* 45:6, 791-92 (June) 1955.

VACCINATION AGAINST PARALYTIC POLIOMYELITIS

PERFORMANCE AND PROSPECTS*

JONAS E. SALK, M.D.

Director of the Virus Research Laboratory, University of Pittsburgh

In the vaccine field trial of 1954, the procedures followed in preparing and administering the vaccines were based on studies which had been carried out by Doctor Salk. Subsequent work in his laboratory, presented in this paper, has made it clear that certain lots of the vaccine, at the time they were used in the field trial, had deteriorated in potency through the effect of merthiolate, which had been added as a preservative.

Further studies on the spacing of successive doses of the vaccine have also shown that the schedule followed in the field trial (injections

* Abstract of paper presented at Ann Arbor, Mich., April 12, 1955, and published in *American Journal of Public Health* 45:5, 575-596 (May) 1955.

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at 0, 1 and 5 weeks) was not the optimal. Doctor Salk now recommends for 1955 a primary vaccination of 2 injections, separated by an interval of 2 to 4 weeks, and that this be followed by a booster injection at an interval not shorter than 7 months.

This paper was written before the appearance of Doctor Francis' report, and therefore without reference to the degree of protection actually demonstrated for any of the vaccines used in the field trial. It is concerned with the quality and performance of vaccines as judged by the antibody response. In this abstract, only the general nature of the experimental evidence can be indicated. The original paper includes twenty charts of supporting data, which are here omitted.

METHODS OF STUDY

It is noted that the antibody response to a given vaccine in laboratory animals differs both in time course and in degree from that observed in man. Consequently it was necessary to study the response in man directly before monkeys or mice could be used intelligently for the assay of vaccines designed for human use; and the optimal spacing of successive doses must be determined directly by trial in man.

It is also noted that the antibody response in man, to each constituent of the trivalent vaccine, is markedly influenced by the presence of homotypic or heterotypic antibody already acquired naturally. Most of the studies included in this paper were carried out on subjects initially without antibody for any of the three virus types.

VACCINES USED IN THE 1954 FIELD TEST

Results of antigenicity tests on monkeys are shown to illustrate the loss of potency in the presence of merthiolate. Parallel tests were made on merthiolated and non-merthiolated samples of nine vaccine lots after varying periods of storage under refrigeration. Three lots had been stored for 3 months, three for 6 and three for 8 months.

Potency of the merthiolated was less than that of the non-merthiolated samples, and the difference of potency increases with time of storage. The loss of potency was most rapid in the Type 1 component, but at 8 months the merthiolated samples were nearly or completely inactive in respect to all three component types. It is noted that deterioration under the influence of merthiolate takes place more rapidly at higher temperatures.

Potency tests had been carried out in monkeys on the vaccines used in the field trial. These tests were done after the addition of merthiolate, but before there had been any appreciable time for deterioration. Data on the antibody response, to each component, are shown for 14 different lots of vaccine. All of them met the minimum potency requirements that had been prescribed, and showed substantial activity.

The same vaccines were tested on human subjects somewhat later, just before or about the time of their use in the field trial. Each was administered in 2 doses to a group of 10 to 43 subjects with no initial antibody of any type. Response to each of the 3 components varied from one lot to another, but certain lots were markedly deficient, particularly in respect to Type 1. Lot 506 evoked only a slight antibody response, and with lots 502, 503 and 507 there was none.

The final set of data on these 14 vaccines shows the response of monkeys vaccinated with non-merthiolated samples of each. All showed satisfactory potency, including those which, after addition of merthiolate, had failed to evoke Type 1 antibody response in man.

In vaccines that have been prepared for use in 1955, the deleterious effect of merthiolate has been avoided, either by substitution of a different preservative or by addition, with merthiolate, of another chemical (versene) which prevents its destructive effect upon the antigen.

Protection of the antigen by versene is illustrated in a chart showing the antibody response in 45 human subjects to a 1955 vaccine, prepared without merthiolate, and for comparison the response in 35 subjects to the same vaccine with added merthiolate plus versene. The difference of potency between the two preparations is insignificant. The same chart shows the response of two groups of subjects to lot 506, used in the 1954 field trial. Without merthiolate, it evoked a satisfactory antibody response; with merthiolate (but without versene) it showed only a trace of antigenic effect.

Another chart shows comparative tests, in man, of 7 lots of vaccine used in the field trial of 1954 and 7 lots prepared for use in 1955. Performance of the 1954 vaccines is shown to be highly irregular, with 3 relatively inactive. The 1955 vaccines are all of high and more nearly uniform antigenic potency.

TIMING OF SUCCESSIVE DOSES OF VACCINE

Doctor Salk presents data on two groups of subjects, all of whom received three injections of vaccine closely spaced in time. In one group the injections were given at 0, 2 and 4

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weeks; in the other at 0, 2 and 5 weeks.

Antibody levels against each virus type were measured two weeks after each of the three doses of vaccine. In these subjects there was a sharp rise of antibody titer after the first dose, continuing after the second, but with little or no additional effect from the third dose. Another chart shows the antibody response in two groups of subjects to primary vaccination (3 doses); the persistence of antibody of all three types, though with a slow decline, over the ensuing 10 months; and finally the effect of a single booster injection at the end of the 10-month period.

The booster injection was followed by a rapid and extensive rise of antibody. Primary vaccination of one of the subject groups was with vaccine 303, of good quality. The other received vaccine 507, of lower potency and particularly deficient in Type 1 antigen. Primary vaccination in the latter group produced practically no Type 1 response. The booster injection, with a potent vaccine, elicited typical booster responses in this group to Types 2 and 3, but a smaller response to Type 1, similar to the effect of a primary vaccination.

Doctor Salk suggests, on the basis of observations of this kind, that primary vaccination has a dual effect. One is the early production of antibody at a moderate level. The other is to bring the immunologic mechanisms of the body into a reactive state, enabling them to respond rapidly and strongly to subsequent stimulation by the same or a related antigen. In this connection it is noted that subjects who have naturally acquired antibody against one type of poliomyelitis virus, on vaccination with a heterotypic vaccine, respond more quickly, and with a higher titer, than do subjects with no initial antibody of any type.

It is suggested that considerable time is required to bring the immunologic mechanisms into the reactive state. Hence the response to the third injection, in a course of vaccination, is most marked if it is given at an interval of several months after the primary stimulation.

COMPARISON OF FIRST DOSE RESPONSE ON ADMINISTRATION BY DIFFERENT ROUTES

Data are given on the antibody response to a single dose of vaccine in three groups of subjects, inoculated respectively by intramuscular, subcutaneous and intradermal injection. Subjects vaccinated intradermally received only 0.1 ml, the others 1.0 ml. Mean antibody titer reached was highest for the group vaccinated intramuscularly, slightly lower with subcutaneous, and still lower with intradermal vaccination.

Considering that the intradermal dose was only 1/10th of that given intramuscularly, it appears that intradermal vaccination is at least as effective as intramuscular. These data are presented with the suggestion that in certain situations other routes of vaccination than the intramuscular may be used.

The provoking effect of certain non-specific injections on paralytic poliomyelitis is well known, and there is some evidence that this effect is most likely to occur with intramuscular injections.

ANTIBODY RESPONSE TO VACCINATION AND INFECTION

One chart shows maximal antibody levels attained in three groups of subjects. One group consisted of patients with acute poliomyelitis, resulting from known Type 1 infection, whose antibody titers were observed at one-week intervals following onset.

The other two groups were subjects, initially without antibody of any type, who received a primary course of vaccination resulting in moderate antibody levels. Of the latter two groups, one (29 subjects) experienced inapparent poliomyelitis infection at some time within the ensuing 10 months, revealed by tests on serum samples obtained at the end of that period. Each of this group showed a marked rise of titer, against one virus type (1, 2 or 3) over the post-vaccination level. The third group showed simply the effect of primary vaccination followed by a single booster injection at 10 months, with no evidence of intervening infection.

Maximal antibody levels attained were high in all three groups, ranging from 64 to above 8192. Mean levels were somewhat higher in the vaccinated groups, however, than in the group whose antibody response was induced by paralytic infection alone.

Doctor Salk proposes that for the year 1955 the vaccine be administered in two doses, separated by an interval of 2 to 4 weeks, to be followed by a third dose after an interval of not less than 7 months, but before the 1956 poliomyelitis season. He further recommends that all children who received the field test vaccines in 1954 be given a booster dose in 1955; and that children who were inoculated with vaccines that performed poorly in

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1954 should receive two doses in 1955, followed by a third dose in 1956.

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POLIOMYELITIS VACCINATION*

ALEXANDER D. LANGMUIR, M.D.,

Chief of the Epidemiology Branch, Communicable Disease Center, Public Health Service

The achievement of the new poliomyelitis vaccine is truly a great story deserving the full play it has received in the newspapers. It is one of the great public health events of the mid-century. It represents a triumph of basic research and an amazing example of effective teamwork.

The details of the evaluation of the 1954 field trial of the Salk vaccine, reported at the University of Michigan, April 12, have been adequately covered by the press. So I thought it would be more interesting to trace some of the scientific problems that had to be solved in the course of achieving a poliomyelitis vaccine and to attempt to outline some of the future developments and problems.

Until quite recently no coherent theory of the disease was established. The scientific basis for an effective means of immunization or control did not exist. Many facts were known, but they were separate pieces of a jigsaw puzzle that did not seem to fit together. For example, early epidemiological studies 50 years ago led to the inference that there were 100 persons infected for each one paralyzed, but it was not until 1940 and later that this thesis was proved in the laboratory. The age distribution of cases, resembling that of measles, led to the inference that immunity followed an attack, but there were disconcert-

* Presented as a summary of Dr. Langmuir's informal remarks before the meeting of the Departmental Council of the Department of Health, Education, and Welfare, April 14, 1955.

Reprinted from *Public Health Reports* 70: 5, 471-472 (May) 1955.

ing numbers of *bona fide* instances of double attacks of the paralytic form of the disease. This cast doubt on the immunity mechanism.

For many years it was believed that the virus had a peculiar predilection for nerve tissues. This belief led to the study of nasal sprays in an attempt to 'block' the supposed pathway to the brain along the olfactory nerve. The treatment caused a lot of people temporarily to lose their sense of smell but did not prevent polio.

Careful search for the virus in the blood failed to reveal its presence there with sufficient consistency to support the conclusion that blood was the mechanism for transfer of the virus to the brain.

In the laboratory for more than 30 years, the only animal susceptible to the infection was the monkey. In 1939, Dr. Charles A. Armstrong of the Public Health Service announced the isolation of the Lansing strain in mice, but this culture turned out to have so many peculiarities that some persons doubted for a time that it was truly a poliomyelitis virus. Tests for immunity to poliomyelitis viruses were very difficult, expensive, and often so inconsistent as to result in continued confusion.

In the field, epidemiological studies also left many points uncertain. The isolation of the virus from feces led many workers to think of the disease as comparable to typhoid. Later, the discovery of the virus in flies led to extensive attempts to control epidemics with DDT. The exact route of infection from one person to another remains in doubt, but increasing evidence points to the similarity of this infection to the other classical contagious diseases such as measles, chickenpox and mumps.

In the solution of these problems, certain major 'breaks' in the form of new discoveries and contributions to basic knowledge deserve special mention.

In 1948, Drs. Howard A. Howe, David Bodian and Isabel M. Morgan, at Johns Hopkins University, were able to define the immunity mechanisms in poliomyelitis by using large numbers of monkeys almost to the degree that other laboratories might use mice or guinea-pigs. The availability of such numbers of monkeys was, of course, one of the brilliant contributions of the National Foundation for Infantile Paralysis. It was shown that three distinct types of poliomyelitis existed, each separate from the other. One of these types was the Lansing strain isolated by Dr. Armstrong. The existence of these three types adequately accounted for the occurrence of double attacks of the disease. A comparable experience is that one can catch German measles independently of true measles. . . .

In 1949, Dr. John Enders at Harvard University announced the cultivation of the poliomyelitis virus in human tissue cultures. Later it was possible to grow the viruses abundantly in monkey tissues. This discovery made possible the production of the large quantities of virus, free of undesirable brain tissue, that would be necessary for a national supply of vaccine.

In 1951, when many workers were still thinking of poliomyelitis as primarily a disease of nerve tissues, Dr. David Bodian at Johns Hopkins and Dr. Dorothy M. Horstmann at Yale University simultaneously announced the discovery of the virus in the bloodstream of monkeys and later of man. The key to this fundamental discovery was looking for the virus at the right time, namely, before symptoms developed, rather than after the disease was in full swing. This discovery further gave promise of the probable effectiveness of a poliomyelitis vaccine because immunity in the blood would eliminate virus and probably prevent its reaching the nervous system.

In 1952, Dr. William Hammond at the University of Pittsburgh reported his successful studies of gamma globulin. These further supported the concept that a vaccine would be successful.

Thus, only in the last 3 or 4 years has a coherent theory of the disease been developed and have the technological tools become available to permit in humans large-scale tests of vaccination against poliomyelitis.

In developing the actual vaccine, Dr. Jonas E. Salk of the University of Pittsburgh has been the extremely able executor of all this basic scientific development over many years in many laboratories. As he most aptly stated recently: 'Dr. Enders threw a forward pass and I happened to catch it. He is an accomplished runner'.

The Public Health Service is proud to have had the opportunity of participating in the vaccine evaluation by assigning Epidemic Intelligence Service officers to Dr. Thomas Francis' laboratory and to the collaborating States and research laboratories. They have been some of the soldiers on the team—doing much of the legwork in collecting basic records and specimens. They have contributed considerably to the accuracy and completeness

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of the data and thereby to the confidence in the conclusions that have been reported.

The Biologics Control Laboratory of the National Microbiological Institute, National Institutes of Health, worked closely with Dr. Salk and the participating pharmaceutical houses in developing standards for the vaccine. This laboratory, along with the NIH Rocky Mountain Laboratory at Hamilton, Mont., and the Virus Laboratory of the Communicable Disease Center, in Montgomery, Ala., also participated in the vaccine evaluation.

I expect widespread acceptance of the vaccine this year. A rapid decline in the disease can be looked for. As yet it cannot be concluded whether the virus will disappear from the Nation or whether the infection will continue to spread among the population without causing paralysis in immune persons. If the infection progressively disappears, as I believe it will, then it will be necessary to immunize only a substantial number but not all susceptible persons in the population. If the virus continues to spread, then it will be necessary to exert particular effort to immunize 100 per cent of the population, including adults. In either event, the supply of vaccine should become sufficient and the essential elimination of the paralytic form of the disease can be predicted with assurance.

A PERSPECTIVE ON POLIOMYELITIS PREVENTION*

In the minds of millions of those affected by the press, radio, and television, poliomyelitis vaccine problems are currently uppermost in the field of public health. Indeed, to many lay and professional persons this is the major public health problem at the moment from the standpoint of time, effort, publicity and energy, if not from the standpoint of death or disability. Rather than to harp philosophically and pessimistically on this obvious and transient overemphasis on a single facet of the broad public health spectrum, public health workers might well use this perfectly natural concern of the public with an undeniably spectacular and valuable development in virus immunology to advance the ultimate total cause of public health. Here is an excellent opportunity to demonstrate the value of well-trained, full-time health departments and to advance co-operative arrangements and mutual understanding between the public health physician and the private practitioner —between voluntary and official public health agencies.

A substantial portion of the credit for facilitating and speeding the development of the vaccine belongs to the National Foundation for Infantile Paralysis. Mutual assistance should continue to be the keynote of the relationship between the voluntary and official agencies. The important role in this vaccination program of the official health departments, and especially of those departments with full-time trained personnel, should be made clear to the public. The officials of the National Foundation themselves have set an excellent example in this recognition.

* From an Editorial in *The American Journal of Public Health*, June, 1955.

PART II

ANSWERS TO QUESTIONS

DOSAGE AND SCHEDULE OF ADMINISTRATION

● *What dosage and schedule of administration of poliomyelitis vaccine was used in the 1954 field trial?*

Three 1 cc. doses, injected into the triceps, the second dose being given one week after the first and the third dose four weeks after the second.

● *What is the revised dosage schedule for poliomyelitis vaccine proposed by Dr. Salk in April 1955 and now recommended?*

Two doses of 1 cc. each, the second being optimally given two to four weeks after the first, with a third 'booster' dose of 1 cc. administered at least seven months later. The first dose is a sensitizing dose and evokes some antibody response within 7 to 10 days. The second dose increases the antibody response. The first two doses, therefore, are sufficient to provide a primary immunization equivalent to that evoked by the three-dose schedule in effect during the 1954 field trial.

● *How long after the first injection should the second injection be given to assure antibody response?*

The antibody response will depend upon the mass of the antigen present in the body.

The first 1 cc. injection is a sensitizing injection and the sensitivity it produces is known to last at least a year or longer. Hence a second injection may be delayed at least this length of time and still induce antibody response.

The first injection does not induce enough antibody formation to insure a protective effect against paralytic poliomyelitis. Practically speaking, therefore, to increase the mass of antigen and antibody, the second injection should be given two weeks after the first injection. Until it is given, no protective effect can be counted upon.

When vaccine supplies are freely available, it will probably be good practice to give the first and second injections, spaced two weeks apart, in the early fall, after the height of the polio season.

Then, to provide complete immunization, a third or booster dose of 1 cc. should be administered in the spring or early summer—at least seven months after the first two injections.

● *How soon after immunization does antibody response occur?*

Within 7 to 10 days after the first dose of poliomyelitis vaccine detectable antibodies (in titer of 1:4 or more) are usually found.

When a second dose of poliomyelitis vaccine is given, at least two weeks after the first dose, a comparable rise in antibody titer occurs; it reaches its maximum about two weeks after the second injection. This second injection is preferably given two to four weeks after the first injection. However, delay in giving the second injection will not eliminate the sensitizing effect of the first immunization injection.

A third dose of vaccine given four weeks after a second dose, as was done in the 1954 field trial, adds little or nothing to the primary response effected by the first two doses.

However, when the third dose is given at least 7 months after the first two doses, it produces a booster effect in which a high and rapid rise of antibody titer occurs within 9 days. The antibody titers recorded following booster injections given 7 to 10 months after primary immunization are as high as those observed in patients who have recovered from natural infection with poliomyelitis virus.

● *How soon are booster doses effective?*

A booster dose of 1 cc. given at least 7 months after primary immunization (2 doses of 1 cc. each two weeks apart) induces a rapid antibody response, which reaches a maximum level in 9 days.

● *How should injections be given—intramuscularly or subcutaneously?*

Intramuscular injection in the triceps or deltoid region has most commonly been employed. In Denmark, where approximately 400,000 children were inoculated with a vaccine prepared in that country, interdermal injection was almost exclusively employed.

The same degree of immunity is conferred by correct use of either the intramuscular or subcutaneous route of administration. The vaccine is so non-toxic that even intravenous injection would not be harmful, although it would not be as effective in sensitizing the immune mechanisms as the other routes of administration.

Practical considerations of mass immunization programs may dictate the route of administration of the vaccine. If the subcutaneous route is employed, mass immunizations can be carried out by changing only the needle for each patient.

With intramuscular injection, one should aspirate after inserting the needle to determine whether it has entered a blood vessel. Under this condition a sterile syringe is required for each patient in order to avoid the risk of transmitting infectious hepatitis. However, in a mass immunization program in a child population, in the absence of evidence of infectious hepatitis, the risk of transmitting this disease may be considered as minimal.

● *May poliomyelitis vaccine be given during the poliomyelitis season?*

Yes; and even during epidemics. On this point a committee of physicians and poliomyelitis experts, representing the American Academy of General Practice, the American Academy of Pediatrics, the American Medical Association, the American Public Health Association, the Association of State and Territorial Health Officers, the United States Public Health Service and the Vaccine Advisory Committee of the National Foundation for Infantile Paralysis, came to the following unanimous conclusion on June 18, 1955:

'First of all, poliomyelitis vaccine has been shown to reduce greatly the incidence of paralytic poliomyelitis and particularly the incidence of severe and fatal cases. Secondly, the vaccine is expected to produce some antibody as early as a week to 10 days following the first shot, and even small amounts of antibody may be expected to have some effect in

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preventing paralytic poliomyelitis after this time. For this reason, the onset of an antibody response to the vaccine may eliminate any subsequent provoking effect of the vaccine injection.

'In summary, those at the meeting agreed that the total preventive effect of the vaccine in a period of rising poliomyelitis incidence should be much greater than the possible hazard from the provoking effect of the injection. Those present also concluded that the benefit to be gained by poliomyelitis immunization, in contrast to the small potential risk of provocation, increases in proportion to the severity of the poliomyelitis incidence, since a large number of paralytic poliomyelitis cases should be prevented during the entire period of the epidemic.

'Therefore the slight hazard of provocation is insufficient to limit the injection of poliomyelitis vaccine even in the presence of a rising incidence of poliomyelitis in the community.'

WHO SHOULD GET VACCINE

● *What age groups are candidates for poliomyelitis vaccine?*

On the basis of susceptibility to paralytic poliomyelitis, as judged by the incidence of poliomyelitis in different age groups, the following order of priority for the use of poliomyelitis vaccine may be fairly established:

Years of age	*Percent incidence of poliomyelitis*
1. 5 to 9	27.3
2. Under 5	24.8
3. 10 to 14	15.0
4. 15 to 19	8.4
5. Pregnant women	no data*
6. 25 to 29	7.9
7. 20 to 24	6.5
8. 30 to 34	5.2
9. 35 and older	4.9

The incidence of poliomyelitis in persons over 20 has been increasing since 1944. The disease has been reported in patients as old as 60.

Immunization of infants under 6 months of age is needless and not recommended. The newborn infant has an inherited or passive immunity from maternal antibodies for approximately six months after birth. When plentiful supplies of vaccine are available and immunization becomes a routine procedure, infants should be inoculated between 6 months and one year of age. Polio immunization will probably be given in conjunction with other established pediatric prophylactic procedures —smallpox vaccination and diphtheria-pertussin-tetanus inoculations.

● *Should vaccine be given to individuals who have recovered from poliomyelitis?*

Yes. Recovery from infection with one type of poliomyelitis virus does not confer immunity to the other two types. Therefore, on the side of more assured protection from subsequent paralytic infection, the recovered patient is still a candidate for a trivalent vaccine. Theoretically, the vaccine would not need the antigens provided by the type of virus with which the patient was infected and from whose effects he has recovered. Practically speaking, however, the usual trivalent vaccine would be used, since two-type virus vaccines have not been prepared.

VACCINATION DURING PREGNANCY

● *Should poliomyelitis vaccine be given during pregnancy?*

Yes. The pregnant woman is approximately twice as susceptible to paralytic poliomyelitis as the non-pregnant woman of the same age group. Furthermore, the severity of the disease seems to be increased during pregnancy. Routine inoculation of the pregnant woman whose period of gestation extends into the polio season may therefore be recommended.

Complete immunization during pregnancy would further enhance the passive immunity of the newborn infant. There is no reason to suppose that immunization with an inactivated virus would harm the fetus.

● *Does the pregnant woman have less immunity to poliomyelitis; that is, is she affected more often than other women of her age group in the general population?*

The pregnant woman seems to be about twice as likely to contract poliomyelitis as the non-pregnant woman of the same age group. The reasons for this probably include both the stress of pregnancy itself and the epidemiological fact that the pregnant woman may be more subject to contact infection from other children already in the family.

The pregnant woman does not apparently

* However studies show that pregnant women are approximately twice as susceptible to paralytic poliomyelitis as non-pregnant women of the same age groups.

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have any less immunity than women of the same age, and immunity in this group depends upon previous poliomyelitis virus infection, which infection for the most part represents a silent infection without the individual showing signs of the disease. In other words, most adults give evidence of such silent infection to at least one type of poliomyelitis virus in roughly ninety per cent of the cases, with thirty to forty per cent giving evidence of immunity to all three types.

● *Is poliomyelitis in the pregnant woman more apt to be fatal than in the non-pregnant woman of her age group? Is poliomyelitis in the pregnant woman more apt to be followed by more serious residual paralysis?*

Just as tonsillectomy, chilling and fatigue and the possible parenteral injection predispose to paralytic attacks of poliomyelitis if virus is present at the time, so does pregnancy seem to be a factor which predisposes to the development of paralytic infection.

Poliomyelitis, like other communicable diseases of 'childhood', seems to be more severe when occurring in the adult as compared to the child. Just as the disease is more serious in the adult, it follows that the mortality rate in adults is also higher than in lower age groups.

Similarly, the older the individual is at the time of a paralytic attack of poliomyelitis, the more extensive the paralysis and the greater the residual after-effects are likely to be.

● *Is there an age factor or does pregnancy alone determine the hazard of the pregnant woman with respect to poliomyelitis and therefore the urgency of vaccinating her against the disease?*

Age of the woman at time of pregnancy does not seem to be important in itself, except that the older the individual at the time of pregnancy, the more likely that individual is to have had previous inapparent infection. It would also seem to be fairly well established that women in the third trimester of pregnancy are slightly more susceptible to paralytic poliomyelitis than they are in the first or second trimester.

● *Have there been any untoward effects noted if the vaccine is given in the first trimester of pregnancy?*

None have been reported to date and there is no theoretical reason for believing that the vaccination procedure would have any deleterious effect upon the fetus.

CONTRA-INDICATIONS

● *Are there any contra-indications to the use of poliomyelitis vaccine?*

Yes.

1. The vaccine should not be given during acute illness.

2. It should not be given to individuals who are exhibiting symptoms of minor illness, especially fever, sore throat or gastro-intestinal upset. These contra-indications apply to any immunizing biological.

3. The vaccine should not be given to individuals in a household where a case of poliomyelitis has just occurred. The chances are that by the time the case is diagnosed, almost all other members of the household will already and currently be infected with poliomyelitis virus. Hence an injection at this time may provoke paralysis.

● *What is the relationship of poliomyelitis immunization to tonsillectomy and adenoidectomy?*

It has been definitely established that previous tonsillectomy increases the risk of serious bulbar poliomyelitis in patients who are infected with the poliomyelitis virus. Insofar as tonsillectomy and adenoidectomy are elective procedures, it is therefore still recommended that they not be performed during the polio season.

A considerable, though varying, degree of protection against bulbar or other paralytic forms of poliomyelitis among patients who must undergo tonsillectomy or adenoidectomy can be provided by immunization *before* the contemplated surgical procedure. The surgery should be postponed in such cases for at least two weeks after a second injection of 1 cc. of poliomyelitis vaccine, to be given two to four weeks after a first injection of 1 cc.

The following answer to this question was given in the *Journal of the American Medical Association*:

POLIOMYELITIS VACCINE AND TONSILLECTOMY

To the Editor: *Is it advisable to perform a tonsillectomy and adenoidectomy on children taking the Salk vaccine or who intend to take the vaccine for poliomyelitis?*

M.D., Selmer, Tenn.

Answer: On the basis of available evidence that tonsillectomy may have a provocative effect on poliomyelitis, it would seem wiser that a child who is to have a tonsillectomy should be given the course of vaccine before the tonsillectomy is undertaken.

From "Queries and Minor Notes"—*Journal of the American Medical Association* 158:7, 619 (June 18) 1955.

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MINIMAL REACTIONS TO VACCINE

● *How prevalent are reactions following the administration of poliomyelitis vaccine?*

Untoward reactions following the administration of poliomyelitis vaccine have been minimal. This matter was thoroughly explored by the Poliomyelitis Vaccine Evaluation Center and presented by Dr. Thomas Francis in his summary report of April 12, 1955. There were no major reactions that could be attributed to the vaccine.

A number of 'minor reactions', such as fainting, nausea, dizziness, slight rash and cold, were reported in 0.4% of the 219,211 children in placebo control areas of the 1954 field trial who actually received vaccine. *But* exactly the same percentage—0.4%—of the 209,806 children in these areas who received placebo injections also reported minor reactions.

So-called major reactions were more prevalent among children receiving placebo than among those receiving vaccine. These major reactions among vaccinated children were not considered to be in any way associated with the vaccine.

Experience in the 1955 vaccination program has not been evaluated in the same way as the data collected from the 1954 field trial evaluation; but there is no reason to believe that the incidence of reactions to properly prepared vaccine was any higher in 1955 than in 1954.

● *Will the antibiotics in the vaccine cause allergic reactions?*

This is a theoretical possibility, but it has not worked out that way in practice. The amount of penicillin remaining in the final vaccine is at most 10 to 15 units per ml. in some lots.

Skin rashes have been observed in a few children who received the vaccine and this has been attributed to the presence of antibiotics to which the children had a pre-existing allergy. Anaphylactic reactions of serious nature have never been observed following vaccine administration. Even when the vaccine was administered to children with known penicillin sensitivity, they did not develop immediate reactions.

A specific experiment in which the present polio vaccine was administered to 63 patients known to be highly allergic to many substances revealed that allergic reactions to the vaccine are minimal and need not be worried about.

In some extremely sensitive individuals a physician may wish to do a skin test prior to giving the vaccine.

Siegal's investigations, however, demonstrate that the vaccine should offer no hazard either to persons allergic to penicillin or as a source of newly-acquired penicillin sensitization.

● *Will poliomyelitis vaccine cause kidney damage?*

The fact that monkey kidney tissue is used to culture the poliomyelitis virus used in vaccine manufacture gave rise to this fear. It has proved groundless. Careful study of reactions among children vaccinated during the 1954 field trial failed to indicate any apparent relationship of vaccination to kidney disease. There is no reason to believe that kidney damage will occur. An exhaustive study of 15 vaccinated individuals and a group of control subjects (by Neva and Salk), using daily Addis counts and other procedures, failed to reveal any kidney damage.

Although the finished vaccine contains traces of kidney protein, these are minimally small quantities. According to manufacturing protocol, tissue culture fluid suitable for further processing must contain less than 0.35 mgm. of total nitrogen per ml., less than 0.2 mgm. of amino nitrogen per ml., and less than 0.02 mgm. of protein nitrogen per ml. Actually most of the nitrogen content of the vaccine is supplied by the nutrient fluid used in the tissue culture process. This fluid (Mixture 199) contains approximately 0.25 mgm. of total nitrogen per ml. and 0.12 of amino nitrogen per ml.

● *Will the use of poliomyelitis vaccine produce Rh sensitivity?*

No, as noted below.

SALK POLIOMYELITIS VACCINE AND THE RH FACTOR

To the Editor: *Has anyone proved that the Salk poliomyelitis vaccine will not sensitize Rh-negative individuals to the Rh factor? Some authorities seem to find that the Rh substance is widely distributed in the tissues as well as in red blood cells. It would seem possible that the Rh factor might be encountered in the kidney cells of the rhesus monkey (on cultures of which the poliomyelitis virus is grown) as well as in the monkey's red blood cells. One assumes that some tissue as well as virus gets in the vaccine, and I wonder if the formaldehyde treatment that allows the preservation of antigenicity of the virus might not also allow the preservation of antigenicity of the Rh substance.*

M.D., Oregon.

Answer: The statement that the Rh substance is widely distributed in the tissues has no sound scientific basis. As pointed out by A. S. Wiener (An Rh-Hr Syllabus, Modern Medical Monographs, vol. 9, New York, Grune & Stratton, Inc., 1954, p. 46), carefully controlled experiments do not show the presence of Rh antigen outside of the red blood cells. Reports in the literature to the contrary may be ascribed to misinterpretation of artefacts that occur so frequently in these delicate tests, to inadequate controls, and to the failure to use the blind technique. With regard to the suggestion that injections of poliomyelitis vaccine might give rise to Rh sensitization in Rh-negative individuals, one may safely predict that this will never occur. For further details consult Queries and Minor Notes (J.A.M.A. 155:1020 (July 10) 1954), where this question has already been discussed in detail.

From "Queries and Minor Notes"—*Journal of the American Medical Association* 158:5, 440 (June 4) 1955.

FACTORS AFFECTING IMMUNITY

● *How long does immunity last?*

This question is still unsettled and subject to much current research. The immunity produced by the two initial injections of 1 cc. each spaced two to four weeks apart is temporary and must be fortified with a booster dose, given at least 7 months later. With the booster dose it seems probable, though it is not yet proved, that immunity may be established for a matter of years.

● *Will immune globulin interfere with immunization by the vaccine?*

The available evidence indicates that gamma globulin, if injected at a different site, will not interfere with antibody response to the vaccine. There is interference, however, if the gamma globulin and vaccine are introduced as a mixture.

● *Will the presence of naturally acquired immunity against one type of virus impair results obtained with the vaccine?*

Not at all. The trivalent vaccine will have a booster effect on antibodies of the type for which immunity from naturally acquired infection exists and it will evoke the development of antibodies to the other two types in the usual manner.

● *Is there a simple test to determine immunity to poliomyelitis?*

No. The only tests available are so complicated and cumbersome that it is simpler and cheaper to immunize the person against paralytic poliomyelitis than attempt to find out whether he is already immune to all three types of virus capable of causing the disease. The average clinical laboratory is not equipped to do the tissue culture and animal inoculation tests by which immunity to poliomyelitis can be determined.

It is possible that a simple test will be developed in the future; but research in this direction is not especially promising.

PROBLEMS OF VACCINE MANUFACTURE AND STORAGE

● *Does poliomyelitis vaccine contain a preservative?*

Yes, and this preservative is stated on the label. Addition of a preservative was made mandatory by amended regulations of the minimum requirements for poliomyelitis vaccine issued May 26, 1955. Up to that time the use of a preservative in the vaccine was optional. The preservatives used in the final vaccine are: Thimerosal combined with sodium ethylenediamine tetraacetate; benzethonium chloride; or methyl paraben and propyl paraben combined.

● *Does the preservative impair the potency of the vaccine?*

The preservatives now in use, with stabilizers, do not impair the potency of the vaccine. However, it may be noted that merthiolate used as a preservative without stabilizer was shown to reduce the antigenic potency of certain lots of vaccine manufactured for the 1954 field trial.

● *Why are antibiotics added to the vaccine during manufacture?*

The purpose of the antibiotics is to prevent bacterial contamination during the tissue culture process. It is common manufacturing practice to add 200 units of penicillin per ml. and 200 mcg. of dihydrostreptomycin per ml. to the tissue culture fluid. The fact that bacterial contamination can be controlled with antibiotics is one of the practical, technical advances that makes large-scale processing of the poliomyelitis vaccine feasible.

● *What is the dating on poliomyelitis vaccine?*

Under the present protocol, vaccine carries an expiration date of not more than six months after the date of manufacture or the date of issue. The date of issue is not more than three months after the date of manufacture, which is the date of release by the National Institutes of Health.

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● *How should poliomyelitis vaccine be stored?*

Under refrigeration at 35 degrees to 50 degrees Fahrenheit, the lower limit being preferable. The vaccine should not be frozen.

● *Would a year's delay in undertaking a nationwide vaccination problem have eliminated the risk of accident in vaccine manufacture?*

There is no guarantee that delay in introducing the Salk polio vaccine in 1955, following the massive field trials in 1954, would have eliminated all risks in its manufacture. The same problems might have been brought to light a year later.

Accidents in the preparation of long-established biological products have been known to occur.

There was in effect 17 years of research behind the Salk vaccine, plus the fact that its field testing was conducted on such a comprehensive scale that many years of trial-and-error guesswork in research were telescoped into one massive and statistically significant experiment, the 1954 Vaccine Field Trial.

Medical history records far more grievous accidents in the introduction of new drugs and biologicals than the circumstances surrounding two lots of apparently dangerous polio vaccine among millions of cc. of vaccine safely manufactured and inoculated into millions of children without untoward results. For example, yellow fever vaccine was put into mass production early in the 1940's. The exigencies of World War II prompted its use on a mass scale. Approximately 2,500,000 individuals in the armed forces were inoculated with this vaccine. Approximately 28,575 came down with homologous serum hepatitis, a totally unexpected and unanticipated complication. About 1 in every 87 inoculated individuals were affected. This unfortunate experience led to a revision of the methods for preparing yellow fever vaccine and a safe product was eventually produced.*

RESEARCH PROBLEMS

● *Are there more than three types of poliomyelitis virus?*

Among many hundreds of strains of poliomyelitis virus tested, only three types have been established. Each type is specific. They produce little if any cross-immunity.

● *Is there a 'negative phase' following the administration of poliomyelitis vaccine?*

The following answer to this question appeared in the *Journal of the American Medical Association*:

NEGATIVE PHASE OF POLIOMYELITIS VACCINE

To the Editor: *Is it possible that cases of poliomyelitis following vaccination may have been precipitated in carriers by a negative phase? We heard much of that some 40 years ago when bacterial vaccines were developed and widely tried in all sorts of infections. 1. Does the Salk vaccine induce a negative phase? If so, what is its duration? As I remember, bacterial vaccines had an initial negative phase lasting 24 to 48 hours. 2. If there is a negative phase of longer duration, would it not be better to postpone mass vaccination until next winter?*

M.D., Brooklyn, N.Y.

Answer: 1. There is inadequate information at present to know whether vaccination with inactivated poliomyelitis virus vaccine creates a negative phase. Certain experimental studies are supposed to have suggested this, but there is no precise information. If there is one, it would be expected to be of brief duration since antibody can be observed to develop in four or five days. 2. There are many reasons why vaccination migh better be done in the winter rather than in the poliomyelitis season.

From "Queries and Minor Notes"—*Journal of the American Medical Association, 159*:7, 619 (June 18) 1955.

Dr. Salk reports that studies have been done to determine whether or not a drop in antibody titer occurs after inoculation. If there is any change, it has not been perceptible even in individuals with low levels of antibody.

Antibody level rises rather than declines after the first dose of vaccine. In experimental animals it has been shown that antibody development and resistance to infection occur almost simultaneously.

● *What are the areas where more research is now urgent in the vaccine and the control program?*

The following areas of research deserve and are receiving attention:

1. Duration in years of immunity to the paralytic disease following vaccination.

2. Search for less pathogenic but still highly antigenic strains of virus which might be substituted for those now in use.

* Editorial: Jaundice following yellow fever vaccine. *Journal of the American Medical Association, 119*: 1110, 1942.

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3. Search for stable strains of attentuated virus which could be used as live virus vaccines.

4. Methods of concentrating the vaccine to render the safety test more precise.

5. Search for a stable strain of normal human or primate cells, susceptible to poliomyelitis virus, which will grow continuously in cultures and which would eliminate the necessity of importing monkeys from India.

6. Search for better methods of virus inactivation.

INFORMATION FOR PHYSICIANS

The National Foundation for Infantile Paralysis will continue to provide information for physicians on the Salk vaccine and other developments in the area of vaccine research and poliomyelitis prevention as soon as research and publication makes this information available. Physicians may always address questions to the Medical Department, National Foundation for Infantile Paralysis, 120 Broadway, New York 5, N.Y.

POLIOMYELITIS

G. SELZER, M.B., Ch.B.,

Virus Research Unit, Department of Pathology, University of Cape Town

Until the latter half of the 19th century poliomyelitis was regarded as a rarity, a non-contagious disease probably due to 'teething' or 'foul bowels' and almost limited to infants; hence the name 'infantile paralysis'.

In the past 30 years the general picture has changed and our concept of the disease has altered considerably. To-day it is considered a highly infectious disease, endemic in most parts of the world and affecting older children and adults with increasing severity. Its etiology has been established beyond doubt as a transmissible, filterable agent or virus of which 3 types have now been recognized.

Poliomyelitis dates back to biblical times. Evidence of this was revealed in excavations in Egypt where the stele of the Egyptian priest Ruma (13th dynasty) showed the shortened withered leg so typical of poliomyelitis. A few cases of poliomyelitis were described in the literature from time to time, but the first recognized epidemic of any size occurred in Sweden in 1887 when 44 cases were notified.[1] To-day the disease is world wide in its distribution, with a general tendency to an increase in most countries. There are epidemic years separated by periods of relative quiescence, but fortunately the mortality rate has not increased proportionately. The most serious epidemic in Sweden occurred in 1953 when 5,090 cases were notified.

It was the astute observations of Wickman[2] in the Swedish epidemic of 1905 which drew attention to the non-paralytic cases of poliomyelitis. He even suggested that the non-paralytic form of the disease was the typical one and that paralysis was a complication in the minority of cases. This is now fully appreciated. Only a small proportion of infected persons develop paralysis, usually no more than 1 in 100 and in some cases only 1 in 1,000 or even 1 in 10,000.

IMMUNOLOGICAL TYPES AND PROPERTIES OF THE POLIOMYELITIS VIRUSES

The infectious nature of the disease was demonstrated by Landsteiner and Popper[3] in 1909. These workers produced a febrile illness and paralysis in a monkey by inoculation of an emulsion of the spinal cord from a fatal case of poliomyelitis. The causal agent was subsequently proved to be a transmissible, filterable agent or virus.

It was not until 1939 that the existence of more than one immunological variety was seriously considered. One of the difficulties which delayed experimental work with the poliomyelitis viruses was that the monkey was the only experimental animal then known to be susceptible to the virus. Armstrong[4] in 1939 isolated a virus from a child in Lansing, Michigan which was found to be infective for cotton-rats. From cotton-rats the infection could be carried over to mice. The poliomyelitis viruses were thus divided into 2 big groups—simian strains to which only monkeys and other primates were susceptible and Lansing or murine strains, which in addition would infect rodents.

A variety of popular names was given to the simian strains isolated. Also the murine

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strains have been variously labelled. There was so much confusion in the nomenclature that in 1948 a committee was appointed by the National Foundation of Infantile Paralysis in the U.S.A. to type the strains employed in laboratories. This work was initiated before tissue culture methods were in general use and therefore conducted with monkeys as experimental animals. It was laborious and expensive, but as a result of this intensive work[5] the picture has been simplified considerably. Immunological studies showed that the poliomyelitis viruses fell into 3 distinct groups labelled Brunhilde, Lansing and Leon or types I, II and III.

The Brunhilde (type I) strain originated from a pool of 7 human stools collected in Baltimore in 1939. Each stool had been known to produce paralytic poliomyelitis in monkeys. The original Leon strain was obtained from the brain-stem and the spinal cord of an 11-year-old male child who had died of bulbospinal paralysis in Los Angeles in 1937.

Types I and III viruses could be propagated in primates and type II in primates and rodents. However, recent workers[6, 7] have succeeded in adapting also types I and III to mice.

The classification of poliomyelitis viruses into 3 distinct serological groups, which has now been generally adopted, was based on the assumption that all strains of poliomyelitis viruses are pathogenic to monkeys. However, recently viruses have been isolated in tissue culture from faeces of cases of paralytic poliomyelitis which cannot be placed in any one of the three types.[8] The question arises whether these belong to a fourth type or whether they are not poliomyelitis viruses at all.

Analyses of epidemics have shown that type I virus has been responsible for most major epidemics, type III for an occasional one, but no major epidemic has been attributed to the type II virus.

The virus measures 30mμ in diameter, and is roughly spherical in shape.[9, 10] It is relatively stable in the pH range 1.6 to 10.3.[11] It resists freezing at $-70°$ C and, unlike most other viruses, also at $-20°$ C for 18 months and longer without loss of titre. It can be kept in 50% glycerol saline at 4° C for years. The poliomyelitis virus does not withstand drying in high vacuum from the frozen state. In this respect it differs from most viruses. It is completely resistant to organic solvents such as ether and chloroform.

The virus will remain viable for many months in raw sewage or natural waters provided the temperature is not too high. Carlson *et al.*[12] found that the standard methods applied in water sanitation were ineffective in removing or destroying the virus in heavily polluted water.

Mundel *et al.*[13] examined the virus content of sewage during the course of an epidemic. The virus could not be demonstrated in digested sludge or in the effluent after sand filtration, but was present in raw sludge, the settled sewage and the effluent from humus tanks.

Antiseptics widely used in bacteriological practice are without effect on the poliomyelitis viruses. Hence the usual precautionary methods adopted in the disposal of stools from a case of typhoid fever will not be effective in the case of poliomyelitis. Chlorine is a good disinfectant when correctly applied.[14] Formaldehyde is a valuable substance in destroying the virus, but impurities present (organic material, etc.) may significantly reduce its antiseptic value. For the disinfection of delicate instruments formaldehyde vapour at 50° C is recommended.[15]

Heating is probably the simplest and most effective method of inactivating the virus; 65° C for 30 minutes will destroy it. Pasteurization of milk, such as 30 minutes at 61.7° C gives a reasonable safety margin.[16]

The Growth of Poliomyelitis Viruses in Tissue Culture: It is a characteristic of all viruses that they will multiply only in living cells. Until recently investigators had to rely on monkeys and mice for the cultivation of poliomyelitis viruses. In 1936 Sabin and Olitsky[17] propagated a poliomyelitis virus in cultures of human embryonic brain tissue and a few years later Burnet and Jackson[18] obtained evidence of viral multiplication in cultures of human pharyngeal and embryonic intestinal tissue; but it was the work of Enders and his colleagues in 1949 which proved conclusively that the poliomyelitis virus could be grown successfully and easily in tissues of extraneural origin. This, the most important recent contribution to the work on poliomyelitis, has proved an invaluable simple and economic tool for the isolation and typing of these viruses, for an analysis of their behaviour and for the production of a vaccine.

There are 2 general types of tissue culture techniques, both of which are used in the study of the poliomyelitis viruses. One, the 'suspended-cell' technique, consists of placing finely minced fragments of tissue in small flasks, covering them with a shallow layer of

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nutrient medium and leaving them to grow at 37° C. The other, the 'fixed-cell' procedure, is the one in more general use to-day. Here the fragments of tissue are planted in a test tube in a thin layer of plasma which is clotted by the addition of embryo extract, or the cells are allowed to grow directly on the glass wall without the addition of clotted plasma. A nutrient medium is added which is changed periodically. In the so-called 'roller-tube' technique the tubes containing the tissue explant are incubated in a horizontal position in a slowly rotating drum. Thus the tissues are alternately covered by medium and exposed to the air in the stoppered tube. Not only does this result in very good growth but the tissues can be examined under the microscope and growth and degeneration of cells can thus be assessed. When the tissues have grown adequately (usually 4-7 days), the virus inoculum is added and the cells observed for degenerative changes (the 'cytopathogenic' effect) which occur within a few days. This cytopathogenic effect can be prevented by adding the homologous serum and can thus be used for typing the strain of virus.

Despite the fact that the Lansing strain is pathogenic to mice, poliomyelitis viruses will only grow in human or simian tissues. Various tissues have been used. These include human embryonic skin, skeletal muscle, intestine and brain; post-natal tissues such as human prepuce, myometrium and monkey testis and kidney.

In roller-tube culture the best results are obtained with human embryonic skin-muscle and post-natal human and simian kidney and simian testis. Kidney tissue is probably the most satisfactory as the growth of cells is good and the yield of virus is high.

For the diagnosis of poliomyelitis the stool or pharyngeal secretions are emulsified in a suitable diluent, centrifuged at 3,000 r.p.m. for 1 hour to remove gross particulate debris, antibiotics added to inhibit bacterial contaminants and then inoculated into the tissue culture tubes. These are observed for the characteristic cytopathogenic effect. If the latter occurs, the fluid from the primary cultures is collected and the virus present identified by neutralization tests. In such a test sets of tissue culture tubes receive inocula of the virus previously mixed with the type specific immune sera. The type of the virus is shown by the serum which prevents the typical cytopathogenic effect.

Recently the poliomyelitis viruses have been propagated in malignant cells derived from a squamous carcinoma of the cervix and maintained in continuous, serial culture for years.[19] These cells, designated the HeLa strain, are of value because of the ease with which one can maintain a constant supply of them for the growth of the viruses.

PATHOGENESIS AND EPIDEMIOLOGY OF POLIOMYELITIS

It is generally accepted that the portal of entry of the virus is the mouth and alimentary tract, but its exact site of multiplication is not known. That it multiplies somewhere in the alimentary tract is suggested by the prolonged excretion of virus in the stool after the onset of recognizable symptoms and by the fact that virus has been recovered from the stools of contacts for several weeks. Experimentally certain species of monkey and chimpanzee can readily be infected by feeding the virus to them. The fact that they have acquired an infection, even if inapparent, can be proved by subsequent development of antibodies even if the virus has not been recovered from the stools.

The virus is excreted from both the pharynx and the intestinal tract in large quantities during the prodromal period and first week of illness. Later it is found in the faeces only, usually from 3 to 6 weeks after the onset of recognizable illness, but may be excreted for a longer period. The virus is not demonstrable in the urine or cerebrospinal fluid. It has been isolated from lymphatic glands at autopsy.[20]

The investigations of Bratt *et al.*[21] for the presence of virus in the stools, as well as antibodies in the serum, in the family associates of 31 households in which clinically recognizable cases of poliomyelitis were present, indicates that the household rather than the individual is the epidemiological unit. They showed that 49% of the household associates were infected concurrently with the patient, and that the proportion varied inversely with the age, ranging from 97% in the 0-4 year age group to 15% in adults. It appears that all the non-immune members of the household are infected simultaneously. Brown *et al.*[22] summarizing available data found that 41% of 324 familial associates of poliomyelitis cases, 20% of 553 non-familial associates and only 3% of non-contacts were excreting virus when tested.

There has been much dispute about the method of dissemination of the virus to the central nervous system. The generally accepted

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view has been that it is spread from the alimentary system via visceral afferent nerve fibres, but recent observations[23, 24] in man and primates suggest that blood dissemination is a likely route. By the time paralysis sets in antibodies are usually present in the blood stream.

Horstmann *et al.*[23] have demonstrated the virus in human blood in association with 3 types of poliomyelitis infection: the minor illness, the asymptomatic infection and preceding the non-paralytic form of the illness. It was demonstrated in 5 of 14 individuals who were bled early enough in the course of infection to be without antibodies. These authors suggest the sequence of events as follows:

First, primary multiplication of the virus occurring during the few days after exposure (and this may be largely or entirely extraneural);

Second, the development of the 'minor illness' in association with the presence of virus in the blood, throat and faeces with viraemia persisting only a few days until antibodies make their appearance;

Finally, if the circulating virus has gained a foothold in the central nervous system, a neural phase of multiplication followed by characteristic signs of central nervous system involvement. However, it must be emphasized that the vast majority of infected persons (about 99% or more) do not reach the stage of central nervous system involvement.

Infection is spread by the contamination of hands and food from pharyngeal secretions or faeces. Although human contact is the usual mode of spread, in some instances flies may be responsible and this may be one of the factors accounting for the seasonal incidence, as the disease is more prevalent in summer than in winter.

Factors Precipitating Paralysis: In recent years it has become apparent that certain factors play a part in precipitating paralysis or localizing it to a particular group of muscles. One such factor is trauma. Thus tonsillectomy and adenoidectomy increase the incidence of bulbar paralysis[25, 26] (as compared with spinal paralysis and non-paralytic cases) if these procedures have been carried out within the previous month. Intramuscular injections, e.g. immunizing injections such as diphtheria may result in the localization of paralysis to the injected limb. Diphtheria-pertussis vaccine in particular has been blamed.[27, 28] However, the danger of diphtheria is probably far greater than that of poliomyelitis; hence it is inadvisable to suspend diphtheria-pertussis vaccine inoculations unless an epidemic of poliomyelitis assumes serious proportions. It is also well recognized that poliomyelitis may run a severe course during pregnancy. That this may be associated with increased adrenal secretions in pregnancy gains experimental support from the demonstration that the administration of cortisone enhances the susceptibility of certain laboratory animals to poliomyelitis.[29]

The part played by fatigue and exertion cannot be over-emphasized. Continued physical activity after the onset of symptoms predisposes the patient to paralysis.[30]

Age: During recent years poliomyelitis has attacked increasingly older subjects and it is known that a higher percentage of deaths occurs amongst adolescents and young adults. According to Paul[31] 40 to 50 years ago the maximum incidence of the disease was in children in the 0-4 year age group. Later it shifted to the 5-9 year group and recently to the 7-15 and 16-25 year age group. It was not until 1930 that the higher incidence in older children became evident.

Immunity: In many parts of the world, especially where the standard of hygiene and sanitation is poor, poliomyelitis is endemic. Infants are infected at a young age; the vast majority develop an inapparent infection and the disease passes unnoticed. Only the occasional child develops the paralytic form of the disease. However, even the symptomless infection with poliomyelitis viruses leaves in its wake a permanent immunity. In some populations infants are infected with two and sometimes three strains of virus in the early years of life so that antibodies to types I, II and III poliomyelitis viruses are present in 80% of the population by the time they reach the age of 5 years.[32] Such an immunity is therefore acquired early, silently and the adults in such a community are not susceptible. In contrast, in countries such as Denmark, etc., the age incidence has shown a significant change. Early childhood infections are rarer so that immunizing infections no longer occur early, and there is a higher incidence of poliomyelitis in older children and young adults.

The question of hygiene and sanitation as factors in the acquisition of immunity is well demonstrated by a comparison of antibodies in the population in Cairo, Egypt and Charlestown, West Virginia, U.S.A. In the former neutralizing antibodies to type II poliomyelitis virus are present in 90% of children by the time they reach the age of 3 years, whilst in Charlestown this figure of 90% is not reached

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until the age of 30 years.[32]

Gear *et al.*[33] have shown that the Bantu acquires antibody in early infancy in the absence of clinical manifestations of poliomyelitis. This is associated with a high incidence of infection as evidenced by the frequency with which virus is recovered from the stools of apparently normal infants.

In the epidemics which occurred in the Union of South Africa in 1945 to 1948 paralytic poliomyelitis was ten times as frequent in the European as in the Bantu and in the latter the majority of cases occurred in children under the age of 5 years.[34]

In countries with modern hygienic arrangements the chance of infection with the poliomyelitis viruses at an early age diminishes so that there is no immunity. Such persons, when they come into contact with the virus in other parts of the country or elsewhere in the world, develop the disease at an older age and in them it may be more severe. This explains the unexpectedly high incidence of paralytic poliomyelitis among military personnel of western nations stationed in countries with a low standard of hygiene during World War II.

The different epidemiological patterns are well illustrated by a study of the incidence of poliomyelitis on the islands of St. Helena (1946) and Malta (1942-3).[35] On St. Helena all ages were affected and the incidence of paralytic disease was almost evenly spread over the ages from 5 to 20 years, indicating a general lack of immunity of the islanders. On Malta, on the other hand, amongst the 426 Maltese cases there were only 29 in individuals over the age of 5 years, indicating the existence of the virus on the island over the preceding years with the development of immunity of the population. With the appearance of an unduly virulent strain of the virus the brunt of the paralysis fell on the non-immune infants under the age of 2 years.

The effect of dissemination of a virulent strain in a community where poliomyelitis was unknown and immunity therefore absent was well demonstrated in the epidemic of 1948-9 in the Chesterfield Inlet Settlement in the Canadian Arctic. The epidemic involved 18.5% of the entire population with paralytic disease, attacking all age groups, including infants.[36]

The evolution of the disease in Israel in recent years is of considerable interest and illustrates the importance of overcrowding. According to Yekutiel *et al.*[37] Israel formerly suffered the commonly encountered mild endemic poliomyelitis. Between the years 1938-49 the number of cases reported annually varied from 20 to 40, except for 70 cases in 1939. Then during the years 1948-51 there occurred a large-scale immigration of people unprecedented in modern history. Thus the Jewish population increased from 717,000 in 1948 to 1,405,000 in 1951. The country was in a state of dire poverty. The economic, social and public health problems were enormous, not the least being overcrowding. The number of cases of poliomyelitis notified in the 6 months July—December 1949 was 108; in 1950 it was 2,618 with a death rate of 12.6% and in 1951 the number was 900. Nearly all the cases occurred in the Jewish portion of the population and were of the infantile type, 61.5% of cases occurring under the age of 3 years, and 85.3% in children under 5 years. The high incidence in children is attributed to the close grouping of infants and small children in the nurseries of the collective rural settlements and camps. The older members of the population escaped, presumably because they were immune. The disease was that of a newly introduced highly infectious one in an overcroweded community in which the passage of infection from group to group was rapid. The circumstances would be appropriate for the emergence of virus strains with exalted virulence. The epidemic with its high incidence of paralytic poliomyelitis in young children is reminiscent of those which were usual 40 years ago.

Antibodies to the poliomyelitis viruses, like other antibodies in man, are transmitted across the placental barrier and are present in the blood of infants for the first few months of life. The question thus arises whether this is a factor causing the inapparent infection seen in the majority of young children. However, Sabin[38] has shown that the rapid rise in antibody titre to type II poliomyelitis virus occurs after 12 months of age. He suggests that in large parts of the world either viruses of low virulence or repeated small doses account for the negligible incidence of paralysis in young children with resultant immunity, and when strains of high virulence appear the incidence of paralysis is greater.

IMMUNIZATION

In 1949 it was shown that gamma globulin prepared from a plasma pool of between 50,000 and 100,000 adults contained antibodies to all three types of poliomyelitis virus. Hammon,[39] who was responsible for the large field trial of gamma globulin, thought that it

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had some effect in diminishing the severity of the paralysis if its onset occurred within a week after receiving the injection. Francis,[40] however, doubts the value of gamma globulin once infection has occurred, but feels it will be preventive if given in a large enough dose in advance of exposure to infection.

There are many shortcomings to the immune serum globulin. The antibody content of each batch would have to be assessed and the dosage varied accordingly; it has only very temporary preventive effects; it is expensive and a wide-scale application benefits only a few.

Active immunization is the only satisfactory method of combating the disease. Whether one produces a vaccine consisting of killed virus or living attenuated (avirulent) strains two essentials must be borne in mind: the vaccine must be incapable of producing paralysis, and secondly, it must produce a satisfactory immune response.

The first poliomyelitis vaccine was produced in 1935 from inactivated infected monkey spinal cord. The vaccine was inoculated into 20,000 children. Twelve developed paralysis as a result of which all attempts at vaccination were discontinued until recently.

In 1953 Salk *et al.*[41] produced a 'killed-virus' vaccine, which was safe in that no cases of paralysis were recorded as a result of the inoculation, and efficacious in that an adequate antibody response was obtained in the serum. This vaccine was produced by the addition of formalin to virus propagated in monkey kidney tissue cultures. Conditions laid down as essential in the preparation of a safe vaccine were: (i) a concentration of formaldehyde of 1 : 4,000, (ii) pH 7.0 and (iii) a temperature of 36° to 37° C for this reaction. If these 3 factors were kept constant then the time required for the destruction of the infectivity of the virus would depend on the concentration of the virus, and the amount of protein present and the time could be estimated fairly accurately.

Isolated cells and cell debris containing adsorbed virus may not be accessible to the formaldehyde and to eliminate this possibility of live virus the fluid was passed through filters which retain bacteria and cells, and permit the passage of virus without loss of titre. Thereafter the virus was inactivated by the addition of formalin. During the process samples of fluid were removed at 24-hour intervals and tested for infectivity. The reaction of formalin was allowed to proceed well beyond the time required to destroy all infectious virus in the volume of fluid being treated with formalin. When this stage was reached sodium bisulphite was added to neutralize the effect of formalin as there is a delicate margin between inactivation of the virus by formalin and destruction of antigenicity. Final tests for safety were then made by inoculation of samples into roller tube cultures of kidney tissue and by intracerebral inoculation of monkeys. These animals were observed for 4 weeks, then killed and the central nervous system examined histologically for signs of infection.

Inherent in the Salk vaccine is the destruction of infectivity and the important question is whether it is still antigenic. Much depends on an initial high concentration of virus.

The antibody response to the Salk vaccine became apparent 6 to 9 days after inoculation of those individuals in whom antibodies were not previously present. In children given 3 injections at intervals of 2 to 3 weeks between them the level of antibody response measured 2 weeks after the third inoculation was comparable to that seen in individuals who had had a naturally acquired non-paralytic infection. After 7 months antibodies were still present but diminished. However, a much better response was obtained if the third injection was given several months later.

In persons who already had immune bodies in their sera (from natural infection) one injection of the vaccine had a booster effect and produced a marked increase in the antibody content of the serum.

It is not yet known how long the antibody response will persist in the Salk-type vaccine nor its capacity to protect from paralysis in epidemics. The statistics gathered from the 1954 study suggested that the vaccine was about 60 to 70% effective against paralytic poliomyelitis with type I infection and 90% effective against types II and III.[42]

The possibility of nephrotoxic effects because monkey kidney is used in the preparation of the vaccine and the possible development of Rh antibodies have been considered, but there is no reason to believe that they occur.

The ideal method of immunization would be the administration of living avirulent strains of the poliomyelitis viruses. These could be given by mouth and mimic the natural infection in man. With the naturally acquired infection specific antibodies are known to be present as long as 40 years after infection.[43]

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Koprowski[44] has fed avirulent strains of type II virus to a limited number of subjects who then developed homologous neutralizing antibodies. More recently Sabin[45] claims to have isolated avirulent strains of each of the three types of poliomyelitis virus. These were administered to 30 human volunteers who possessed no demonstrable antibody for the poliomyelitis viruses. None developed viraemia and in all the infections were asymptomatic. The antibody response was high and, except in the case of type III virus, persisted. The experiment was carried out recently and it remains to be seen how long these antibodies persist.

From available knowledge it appears that the best time to administer such a live attenuated vaccine would be during the first few months of life when protective antibodies transmitted transplacentally are still present, and can be expected to protect the central nervous system from the virus whilst allowing a local intestinal infection to be established.

Of interest is the spontaneously occurring neutralizing substances for the three types of poliomyelitis virus in bovine sera.[46] These substances exhibit the same properties as the antibodies to types I, II and III poliomyelitis viruses in human serum. Virulent strains of poliomyelitis virus fail to produce even inapparent infection in calves. Sabin suggests that cattle might be infected with an agent or agents antigenically related to the poliomyelitis viruses. If those agents could be identified they might prove to be of value in the immunization of Man.

Clinical observations and experimental work in the past 10 years have thrown much light on the problems of poliomyelitis, but many questions still remain unanswered. What are the factors which decide whether the central nervous system will be invaded or not? Why is paralysis more severe in older children and adults than in young infants? Is it possible that inactivation of the virus by formalin in the preparation of the vaccine was not complete and that residual living virus produced the immune response? What improvements can be brought about in the Salk-type vaccine, and will it be replaced in the near future by vaccines of living attenuated viruses? If attenuated strains are used in vaccination how will one ensure they remain attenuated? Above all will it be possible by the use of the vaccine to eliminate paralytic poliomyelitis from a community? To these, and many other problems, the answers are, as yet, not clear.

OPSOMMING

Tot die tweede helfte van die 19e eeu is poliomiëlitis as 'n seldsame siekte beskou. Sedertdien het die opvattings in verband daarmee verander, met die gevolg dat dit vandag beskou word as 'n hoogs aansteeklike siekte wat endemies in die meeste dele van die wêreld is, en ouer kinders en volwassenes steeds ernstiger affekteer.

Wickman was die eerste man wat die nie-verlammende gevalle van poliomiëlitis tydens die Sweedse epidemie van 1905 onderskei het. Sy skrandere waarnemings is allerweë aanvaar, en vandag word daar erken dat nie meer as 1 : 100 (en in sommige gevalle slegs 1 : 1,000 of selfs 1 : 10,000) verlam word wanneer hulle deur die virus besmet word nie.

Sedert 1939 weet ons dat daar ten minste 3 immunologiese tipes van die virus bestaan, nl. Brunhilde, Lansing en Leon (of tipes I, II en III). Tipe I was verantwoordelik vir die meeste groot epidemies, tipe III vir die toevalliges. Tipe II het geen groot epidemies veroorsaak nie.

Die standaard-metodes vir die reiniging van water vernietig nie die virus in ernstige besmette water nie, en die ontsmettingsmiddels wat op 'n groot skaal in die bakteriologiese praktyk gebruik word, het geen effek op die virus nie. Die gewone metodes wat toegepas word vir die wegruiming van die ontlasting van 'n persoon wat aan ingewandskoors ly, sal dus ondoeltreffend wees in gevalle van poliomiëlitis. Chloor is 'n goeie ontsmettingsmiddel as dit op die regte manier aangewend word. Formaldehide is 'n waardevolle middel om die virus te vernietig, maar onsuiwerhede kan die ontsmettingsvermoë daarvan aansienlik verminder. Hitte is waarskynlik die eenvoudigste en doeltreffendste manier om die virus inaktief te maak.

Net soos alle ander virusse groei die poliomiëlitisvirus slegs in lewende selle. In 1949 het Enders *et al.* bo alle twyfel bewys dat die virus op ekstraneurale weefsel gekweek kan word. Ten gevolge hiervan is die isolasie en tipering van die virusse, die produksie van 'n entstof, en die serologiese tipering van die verskillende soorte vereenvoudig. Nierweefsel is waarskynlik die mees bevredigende weefsel-voedingsbodem omdat die selle goed groei en die virusopbrengs hoog is.

Daar word gewoonlik aangeneem dat die mond en die spysverteringskanaal die ingangspoort van die virus is, en hoewel die presiese plek van vermenigvuldiging nie bekend is nie, is dit waarskynlik die spysverteringskanaal. Die virus word in groot hoeveelhede uit die keelholte en die derm afgeskei gedurende die siekte-aankondigende periode en die eerste week van die siekte. Later word dit slegs in die ontlasting aangetref, gewoonlik van 3-6 weke (of langer) na die aanvang van die herkenbare siekte.

Die huisgesin liewer as die individu is die epidemiologiese eenheid, aangesien 15% van die volwassenes en tot 97% in die 0-4-jaar-groep in die huis gelyktydig met die pasiënt besmet kan word. Dit skyn asof al die nie-onvatbare lede van die huisgesin op dieselfde tydstip besmet word.

Die virus versprei waarskynlik na die sentrale senustelsel deur die bloedstroom. Teen die tyd dat verlamming sy verskyning maak, is teenstowwe gewoonlik aanwesig in die bloed.

Die infeksie word versprei ten gevolge van die besmetting van hande en voedsel deur keelafskeidings of ontlasting. In sommige gevalle kan vlieë 'n rol speel. Die seisoensvoorkoms van die siekte

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gedurende die somermaande kan waarskynlik hieraan toegeskryf word.

Sekere traumatiese faktore verhaas verlamming, bv. onlangse tonsillektomie en adenoïedektomie verhoog die voorkoms van bulbêre verlamming. Binnespierse inspuitings kan die verlamming in die ingespuite ledemaat lokaliseer. Difterie-kinkhoesentstof word veral as die sondebok beskou. Aangesien die gevaar van witseerkeel waarskynlik veel groter is as dié wat deur poliomiëlitis meegebring word, is dit onraadsaam om hierdie inentings te staak tensy 'n poliomiëlitis-epidemie ernstige afmetings aanneem.

Swangerskap word ook in verband gebring met 'n baie ernstige verloop van die siekte, en die rol wat deur uitputting en inspanning gespeel word, kan nooit te sterk benadruk word nie. Voortdurende fisiese bedrywigheid na die aanvang van die simptome maak die pasiënt vatbaar vir verlamming.

Steeds ouer persone word tans deur die virus aangeval. Omtrent 40-50 jaar gelede het die siekte veral voorgekom onder die 0-4-ouderdomsgroep, maar dit het verskuif na ouer slagoffers totdat die infeksie onlangs sy verskyning hoofsaaklik onder persone in die ouderdomsgroepe 7-15 en 16-25 gemaak het.

Poliomiëlitis is endemies waar die openbare gesondheidsmaatstawwe laag is. Die oorgrote meerderheid van suigelinge ontwikkel 'n nie-sigbare infeksie, maar slegs hier en daar doen 'n kind verlamming op. Maar selfs die simptoom-lose infeksie laat 'n blywende onvatbaarheid na. Teenstowwe vir tipes I, II en III is aanwesig by 80% van die bevolking teen die tyd dat hulle 5 jaar oud is. In so 'n gemeenskap is die volwassenes nie vatbaar nie. Die Bantoes bou op 'n groot skaal teenstowwe in die vroeë suigelingsjare op, en die virus word gevind in die ontlasting van oënskynlik normale suigelinge. Tydens die Suid-Afrikaanse epidemies van 1945-1948 het daar 10 keer meer gevalle van paralitiese poliomiëlitis onder die blankes as onder die Bantoes voorgekom. By laasgenoemde was die meeste slagoffers onder die ouderdom van 5 jaar. Moderne higiëniese reëlings verminder die kanse op infeksie gedurende die vroeë lewensjare, met die gevolg dat daar geen immuniteit is nie. Die lede van so 'n gemeenskap word derhalwe vatbaar vir die siekte op 'n meer gevorderde leeftyd in ander dele van die land of elders in die wêreld. Dit verduidelik die onverwagte hoë voorkoms van paralitiese poliomiëlitis onder die militêre personeel van die Westerse volke wat tydens Wêreldoorlog II in lande met 'n lae standaard van higiëne gestasioneer was.

Die mate waarin immuniteit voorkom, het 'n betekenisvolle uitwerking op die epidemiologiese patroon van die siekte. Die belangrikheid van oorbevolking word toegelig deur die uitbreek van die siekte in Israel, waar skielike grootskeepse immigrasie, gepaard met uiterste armoede, in verband gebring is met ernstige epidemies van paralitiese poliomiëlitis, veral onder jong kinders—iets wat die toestande van ongeveer 40 jaar gelede sterk in die herinnering terugroep. Die saamhok van suigelinge en klein kinders in die kleuterskole van die kollektiewe nedersettings was bes moontlik ook 'n belangrike faktor.

Die teenstowwe van die poliomiëlitis-virus gaan deur die placenta na die fetus, en word aangetref in die bloed van suigelinge gedurende die eerste paar lewensmaande. Of dit die nie-sigbare infeksie wat by die meeste jong kinders opgemerk word, verduidelik, is nie seker nie.

Gamma-globulien kan infeksie voorkom as dit toegedien word voor blootstelling, maar dit is waarskynlik van geen waarde as die persoon reeds besmet is nie. Dit is duur, en dit het net 'n tydelike effek. Aktiewe immunisasie is die enigste metode om die siekte te bestry. Die entstof (of dit nou al gemaak word van 'n vernietigde virus, of van lewende, verswakte soorte) moet nie die vermoë besit om verlamming te veroorsaak nie, en moet 'n bevredigende immunisasie-reaksie hê. Die entstof wat met formalien inaktief gemaak en van besmette bobbejaan-rugmurg verkry is, het in 1935 12 gevalle van verlamming tot gevolg gehad onder die 20,000 kinders wat daarmee ingeënt is. Dit het alle inentingspogings tot pas onlangs toe stopgesit. In 1953 het Salk 'n veilige en doeltreffende ‚vernietigde virus'-entstof geproduseer, en dit het duidelik geword dat daar 'n delikate grens is tussen die inaktiefmaking van die virus met behulp van formalien, en die vernietiging van die vermoë om teenstowwe te vorm. Die grondbeginsel van die Salk-entstof is die uitskakeling van besmetlikheid, en die belangrike vraag is of dit dan nog die vermoë besit om teenstowwe te vorm.

Dis nie bekend hoe lank die teenstof-reaksie op entstof van die Salk-tipe duur nie. Ons weet ook nie in watter mate dit die vermoë het om persone tydens epidemies teen verlamming te beskerm nie. Daar is geen rede om beskadiging van die niere van die persone wat ingeënt word, te verwag nie, aangesien die virus op bobbejaannier-weefsel gekweek is, en Rh-sensitisasie ook uitgeskakel is.

Ingestie van lewende nie-giftige soorte sal natuurlike infeksie by die mens naboots. Dit sou die ideale immunisasie-metode wees, en voorlopige verslae dui daarop dat spesifieke teenstowwe op hierdie manier ontwikkel kan word. Die beste tyd vir die toediening van 'n lewende entstof sal waarskynlik gedurende die eerste lewensmaande wees, wanneer die teenstowwe wat van die moeder ontvang is, die sentrale senustelsel van die suigeling kan beskerm terwyl die plaaslike ingewandsinfeksie tot stand gebring word.

Die onvermoë om kalwers met die giftige soorte poliomiëlitis-virus te besmet, moet toegeskryf word aan die spontaan voorkomende neutraliserende stowwe teen al drie soorte virus wat in koeiserums gevind word. Dit kan bes moontlik nog van waarde wees by die immunisasie van die mens.

Baie probleme bly nog onopgelos. Watter faktore stel vas of die sentrale senustelsel aangetas sal word al dan nie? Waarom neem verlamming ernstiger afmetings by volwassenes as by kinders aan? Kan die entstof van die Salk-tipe verbeter word, en sal dit in die naaste toekoms vervang word met 'n entstof voorberei van 'n verswakte lewende virus? Hoe moet daar verseker word dat verswakte tipes verswak bly? Bo alles, sal die gebruik van 'n entstof 'n einde aan paralitiese poliomiëlitis in 'n gemeenskap maak? Op hierdie en baie ander vrae is die antwoord nog nie duidelik nie.

I would like to thank Professor M. van den Ende for his helpful criticism.

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PREPARATE EN TOESTELLE

CROMOXIN FORTE

KARBASOCHROOM OF ADRENOCHROOM-SEMIKARBASOON

Cromoxin Forte ('n sintetiese samestelling) verkort die bloeityd, en is ook van nut in asteniese toestande. Dit is 'n oplossing van adrenochroom-semikarbasoon en natriumsalisilaat in water. Die natriumsalisilaat verleen 'n groter oplossingsvermoë aan die adrenochroom wat nie juis baie oplosbaar is nie.

Uitwerking: Cromoxin het 'n regstreekse uitwerking op gekwetste haarvaatjies, en laat hulle terugtrek. Daar is geen gevaar van slagaar- of aarembolie nie, aangesien die middel geen uitwerking op koagulasiemeganismes het nie.

Daar is geen gevaar van 'n styging van die bloeddruk nie, aangesien geen algemene sametrekking van die haarvaatjies plaasvind nie.

Dit stimuleer die sametrekking van die spiere deur invloed op die Cori-siklus uit te oefen, d.w.s. dit belet glikolise, dit oksideer melksuur, en dit bou glikogeen opnuut op (die Pasteur-effek).

Dit het ook 'n ACTH-bevorderingseffek waarvan in die Thorn-eosinofiel-reaksietoets gebruik gemaak word.

Voordele: Adrenochroom kom op 'n natuurlike wyse in alle weefsels voor. Cromoxin het so te sê geen toksiese effek nie. Babetjies en ou mense kan met veiligheid behandel word. Cromoxin begin inwerk 'n paar minute nadat dit toegedien is. Daar is geen kardiovaskulêre bykomstige effekte nie. Dit het 'n gunstige uitwerking op al die verdedigingsmeganismes van die liggaam.

Toediening: Binnespierse inspuiting van 5 mg. 30 minute voor 'n operasie.

Vir die Pasteur-effek kan verdunde Cromoxin binne-aars gedruip word.

Dosisse—Chirurgiese Bloeding: 5 mg. voor die operasie; 5 mg. 12 uur na die operasie.

Indikasies—(a) Hemostaties: (*Medies*). Alle vorms van haarvatsypeling of -bloeding.

(*Chirurgies*). Nie-duidelike operasiegebiede, met bloedsypeling, bv. prostatektomie.

(*b*) *Dinamogenies*: Spanningstoestande; skok (chirurgies en traumaties) en miopatieë (met ongeskonde senuvoorsiening).

Verpakking: Dosies van 3 x 2 k.s. (5 mg.) Cromoxin Forte.

SURFADIL

Eli Lilly International Corporation kondig die beskikbaarstelling aan van:

XUM

‚SURFADIL'-LOTIO

Omskrywing: Iedere 100 k.s. bevat ‚Histadyl' (Tenilpiramine, Lilly) 2 gm., ‚Topocaine' (Siklometikaïne, Lilly) 0.5 gm., Titanium-dioksied 5 gm.

Indikasies: Vir die verligting van nat, vogtige allergiese dermatose en ekseem. Ook nuttig vir die verligting van die plaaslike ongerief wat veroorsaak word deur insekbytplekke en 'n luieruitslag, en wanneer dit ook al nodig is om 'n anestesiese of 'n antihistaminiese effek plus die uitdrogende beskermende uitwerking van titanium-dioksied te verkry.

Kommentaar: ‚Surfadil'-*lotio* is welriekend en vleeskleurig vir kosmetiese keurigheid. Die voordele van titanium-dioksied—bedek die vel vyf maal beter as sinkoksied, chemies en fisiologies onaktief, uitstekende kleef- en hoë absorpsievermoë, weerkaats die strale van die son.

Verpakking: Verkrygbaar in bottels van 2 ons.

NEOGLYCODEN

Petersen Beperk (Barrackstraat 16, Kaapstad) kondig hul jongste hoesstroop—Neoglycoden—aan.

Samestelling: Benewens ander bestanddele bevat hierdie preparaat Folkodine, die algemene benaming van Morfolinieletielmorfine-monohidraat, Efedrine HCl en Chloroform, in 'n swartaalbessie-basis wat besonder aangenaam smaak.

Indikasies: Neoglycoden word aanbeveel as 'n krampwerende middel in gevalle van ernstige of langdurige hoes, aangesien dit doeltreffender as Kodeïne-fosfaat is by die onderdrukking van hoesreflekse. Met Folkodine is daar ook minder maagversteurings as met Kodeïne.

Verpakking: In bottels van vier ons.

Lede van die mediese professie word uitgenooi om om 'n monster te skryf.

VI-DAYLIN-DRUPPELS

Vi-Daylin-druppels: 'n Heerlike, met suurlemoen gegeurde, gebalanseerde diëetaanvulling, spesiaal saamgestel vir suigelinge—vanaf geboorte tot 12 maande.

‚Vi-Daylin-druppels' is 'n kragtige formulering van 7 noodsaaklike vitamines.

‚Vi-Daylin-druppels' meng maklik met vrugtesap, melk of suigelingformules.

Iedere 0.6 k.s. verskaf:

Vitamine A	5,000 eenhede.
Vitamine D	1,000 eenhede.
Thiamine HCl	1.5 mg.
Riboflavine	1.2 mg.
Piridoksine HCl	0.5 mg.
Askorbinesuur	50 mg.
Nikotinamide	10 mg.

‚Vi-Daylin-druppels' is verkrygbaar in bottels bevattende 30 k.s., volledig met 'n gekalibreerde druppelaar.

ENTEROBIOTIESE TABLETTE

Hierdie produk is 'n samestelling van 2 antibiotica wie se bedrywighede teen die gewone ingewandsflora aanvullend is. Iedere tablet bevat 50 mg. Terramycin-hidrochloried en 250 mg. Neomycinsulfaat. Ná mondelinge toediening word die Terramycin in 'n groot mate uit die spysverteringskanaal geabsorbeer. Neomycin word swak geabsorbeer (ongeveer 3% van die hoeveelheid wat ingeneem word, word saam met die urine afgeskei).

Enterobiotiese tablette is nuttig vir die teenwerking van bakterieë in die dikderm tydens operasies aan die grootderm en die anus.

Dosis: Dit verskil na goeddunke van die geneesheer, maar toediening moet nie oor 'n tydperk van meer as 72 uur geskied nie. Aangesien nòg Terramycin nòg Neomycin 'n aktiewe uitwerking op swamme het, is dit moontlik dat daar suurdeeggroeisels sal wees ná vermindering van die bakteriese flora in die dikderm.

Enterobiotiese tablette is verpak in bottels van 40. Prys vir die gebruiker: 190s.

PREPARATIONS AND APPLIANCES

CROMOXIN FORTE

CARBAZOCHROME OR ADRENOCHROME SEMICARBAZONE

Cromoxin Forte (a synthetic compound) shortens the bleeding time and is also of use in asthenic states. It is an aqueous solution of adrenochrome semicarbazone and sodium salicylate. The latter increases the solubility of the very sparingly soluble adrenochrome more readily.

Action: Cromoxin acts directly on traumatized capillaries only, causing them to retract. There is no danger of arterial or venous embolism as there is no action on coagulation mechanisms.

There is no danger of a rise in blood pressure, as there is no generalized capillary contraction.

It stimulates muscle contraction by influencing the Cori cycle, i.e. it inhibits glycolysis, oxidizes lactic acid and resynthesizes glycogen (the Pasteur effect).

It also has an ACTH-promoting effect, made use of in the Thorn eosinophil response test.

Advantages: Adrenochrome occurs naturally in all tissues. Cromoxin is virtually free from all toxic effects. Babies and old people may be treated with safety. Cromoxin takes effect within a few minutes of administration. There are no cardio-vascular side effects. It acts favourably on all the defence mechanisms of the body.

Administration: Intramuscular injection of 5 mg. 30 minutes before operation.

For the Pasteur effect, an intravenous drip of diluted Cromoxin can be administered.

Dosages—Surgical Haemorrhage: 5 mg. before operation; 5 mg. 12 hours after operation.

Indications—(a) Haemostatic: (*Medical*). All conditions of capillary ooze or bleeding.

(*Surgical*). Non-clear operative fields with ooze bleeding, e.g. prostatectomy.

(*b*) *Dynamogenic*: Stress condition; shock (surgical and traumatic) and myopathies (with intact nerve supply).

Packaging: Boxes of 3 x 2 c.c. (5 mg.) Cromoxin Forte.

SURFADIL

Eli Lilly International Corporation announce the availability of:

LOTION 'SURFADIL'

Description: Each 100 c.c. contain 'Histadyl' (Thenylpyramine, Lilly) 2 Gm., 'Topocaine' (Cyclomethycaine, Lilly) 0.5 Gm., Titanium Dioxide 5 Gm.

Indications: For the relief of weeping, moist

allergic dermatoses and eczema. Also useful for alleviating the local discomfort of insect bites and diaper rash and whenever it is desirable to obtain anaesthetic and antihistaminic effect plus the drying protective action of titanium dioxide.

Comment: Lotion 'Surfadil' is pleasantly scented and flesh-coloured for cosmetic elegance. Titanium Dioxide advantages—covers skin five times better than zinc oxide, chemically and physiologically inert, excellent adhesion and high absorbency, reflects sun's rays.

Packaging: Available in 2 oz. bottles.

NEOGLYCODEN

Petersen Limited (16, Barrack Street, Cape Town) announce their newest Cough Syrup—Neoglycoden.

Composition: This preparation contains, among other ingredients, Pholcodine, the generic term for Morpholinylethylmorphine Monohydrate, Ephedrine HCl and Chloroform in a very pleasant-tasting black currant base.

Indications: Neoglycoden is recommended as an anti-spasmodic in severe coughs and coughs of long standing, since it is more effective than Codein Phosphate in surpressing cough reflexes. There is also a lesser degree of gastric upsets with Pholcodine than with Codein.

Packaging: In 4 oz. bottles.

Members of the medical profession are invited to write for a sample.

VI-DAYLIN DROPS

Vi-Daylin Drops: A delicious lemon-flavoured balanced dietary supplement designed especially for infants—birth to 12 months.

'Vi-Daylin Drops' provides a potent, balanced formula of 7 essential vitamins.

'Vi-Daylin Drops' mixes easily in fruit juices, milk or infants' formula.

Each 0.6 c.c. supplies:

Vitamin A	5,000 units.
Vitamin D	1,000 units.
Thiamine HCl	1.5 mg.
Riboflavin	1.2 mg.
Pyridoxine HCl	0.5 mg.
Ascorbic Acid	50 mg.
Nicotinamide	10 mg.

'Vi-Daylin Drops' is supplied in 30 c.c. bottles complete with calibrated dropper.

ENTEROBIOTIC TABLETS

This product provides a combination of 2 antibiotics whose activities are complementary against the usual intestinal flora. Each tablet contains 50 mg. of Terramycin Hydrochloride and 250 mg. of Neomycin Sulphate. Terramycin is absorbed to a considerable extent from the gastrointestinal tract following oral administration. Neomycin is poorly absorbed (about 3% of the amount ingested is excreted in the urine).

Enterobiotic tablets are useful in suppressing the bacteria of the colon in surgery of the large bowel and the anus.

Dosage: This varies at the discretion of the surgeon, but administration should not extend beyond 72 hours. As neither Terramycin nor Neomycin is active against fungi, outgrowth of yeasts may follow reduction of the bacterial flora of the colon.

Enterobiotic tablets are packed in bottles of 40. Price to the consumer: 19os.

NOTES AND NEWS · BERIGTE

Dr. Michael Silver has joined Dr. R. R. Sidelsky and Dr. H. Kretzmer in practice in Bulawayo. His address is 15-18 Marvel Court, Main Street, Bulawayo.

* * *

Mr. Cyril D. Kisner, M.B., Ch.B., Ch.M. (Rand), is now practising as a urologist at 7 Lister Buildings, Jeppe Street, Johannesburg. (Telephones—*Rooms*: 22-1453; *Residence*: 43-5300.)

* * *

Mr. Arthur Helfet, F.R.C.S., of Cape Town (who has been appointed to the Editorial Board of the Post-Graduate Medical Journal in Great Britain) has recently returned from a visit to Israel where he spent a month as guest lecturer delivering lectures, taking seminars and demonstrating operations.

In his work he was associated with the famous Leo Mayer of New York who, at the age of 70, lectures and operates with great mental and physical vigour.

Dr. Mayer is a world authority on tendon surgery and there is particular interest in Israel, under his guidance, in the prevention of deformity after poliomyelitis—a considerable problem as Israel has the greatest endemic rate in the world—a rate which surpasses our own epidemic rate.

Mr. Helfet has been invited with Dr. Mayer to repeat the visit and they propose to do so in 1957.

* * *

Dr. Charles Goldin, M.B., Ch.B. (Wits.), D.O.M.S. (London), late Senior Registrar, Western Ophthalmic St. Mary's Hospital, London, has joined Dr. O. M. Haarburger in practice as an ophthalmic surgeon at 308 Dumbarton House, Church Street, Cape Town. (*Telephone*: 2-6197.)

* * *

Dr. David Ordman, Head of the Vaccine and Allergy Department of the South African Institute for Medical Research, Johannesburg, will attend the Second International Congress of Allergology to be held in Rio de Janeiro from 4-11 November 1955.

Dr. Ordman has accepted an invitation to read a paper at the Congress on the significance of climate in bronchial asthma and its relation to house dust sensitivity. After the Congress he will spend some time in Brazil and the Argentine investigating problems in allergy common to South America and South Africa.

Dr. Ordman, accompanied by his wife, will be away from the Union from 24 October 1955 to mid-January 1956.

* * *

Mr. N. Kretzmar, F.R.C.S., has moved his consulting rooms to Escul House, 88 Dutoitspan Road, Kimberley, where he will continue his surgical practice.

* * *

Dr. Jan Hendrik Louw has been appointed to the Chair of Surgery at the University of Cape Town.

Professor Louw qualified in 1938 as M.B., Ch.B. (Cape Town) and obtained the degree of Ch.M. (Honours) from his *alma mater* in 1946. He obtained distinction in the clinical examination for this degree.

Born at Middleburg, C.P., on 26 May 1915, he

XUM

matriculated (1st class) at the Rondebosch Boys' High School, where he held the first Mason Scholarship. After his medical qualification he was House Surgeon to Prof. C. F. M. Saint and House Physician to Prof. J. F. Brock at the Groote Schuur Hospital.

Prof. Jan Hendrik Louw

Following a short spell in general practice at Bedford in the Cape, Professor Louw joined the armed forces (1941-1945). During this period he was Medical Officer in charge of Surgical Wards at 102 General Hospital, Middle East and at the Military Hospital, Wynberg. He spent 2 years in the desert.

After the war he assisted Mr. J. A. S. Marr and Mr. M. Cole-Rous in private surgical practice. In July 1946 he was appointed Honorary Assistant Surgeon at Groote Schuur Hospital and from 1947-1950 he was Assistant to the Professor of Surgery at the University of Cape Town.

At the end of 1950 he was awarded a Nuffield Dominion Travelling Fellowship which allowed him to spend 1951 in the United Kingdom and Scandinavia doing post-graduate work, with particular reference to children's surgery.

He returned in 1952 to take up a full-time appointment at the Groote Schuur Hospital as Head of a surgical firm which included the children's surgical unit. In addition, he held the position of Senior Lecturer in Surgery and Deputy to the Professor of Surgery in the University of Cape Town.

In 1954 he was appointed Associate Professor of Surgery and, while holding the post of Acting Professor of Surgery (from 1 April 1955), he was appointed to the Chair in August this year.

Professor Louw has made valuable contributions to surgical research. His thesis for the Ch.M. degree (which he obtained with honours) was on *The Morphology of the Main Bile Ducts.* He has also published important papers on congenital intestinal obstruction, thermal burns and the response of newborn infants to major surgery.

POLIOMYELITIS VIRUS

Dr. N. E. McKinnon, Department of Epidemiology, School of Hygiene, University of Toronto, writing in the *Canadian Medical Association Journal* of 15 July 1955, states on p. 154: ... The late Sir John Ledingham, then Director of the Lister Institute and a recognized authority of world-wide repute with the experience of a life-time in this field, was highly sceptical of the value of any dead virus, including that of rabies. Our knowledge of influenza—disease, infection, vaccine, immunity—is so slight that it is surprising that the evidence for its dead virus inducing protection would be considered 'excellent'. A Saskatchewan physician well acquainted with the situation has stated very recently that vaccine for equine encephalitis has not proved reliable; thus there would seem to be reason to doubt the evidence for dead virus inducing protection in that infection. Although some authorities once thought otherwise, dead vaccinia virus has failed entirely to induce protection. Effective louping-ill vaccine, though often supposed to be dead, contains live virus. Dead virus did not induce protection against yellow fever; nor was it acceptable in dog distemper. Any authority could list other similar examples. For a few days, and in spite of some slight incongruities lacking a completely satisfactory explanation, it looked as if it could be safely inferred from the superb analysis of Dr. Francis that dead poliomyelitis vaccine could give protection, though not of the 10 : 1 order afforded by diphtheria toxoid; but the subsequent experience should at least suggest the need for further consideration. As Dr. Evans pointed out (*Canad. Med. Assoc. J.*, 1955, **72,** 863), the presence of demonstrable antibody, even neutralizing antibody, does not necessarily mean protection. Macleod (*J. Hyg.*, **52,** 9, 1954) has shown that even good protection in the laboratory animal against parenteral challenge (in *Typhi murium* infection in mice) does not necessarily indicate protection against natural infection; this fundamental finding may well be of high significance in the polio problem. At the moment we only know that poliomyelitis virus can be killed so that it will not produce poliomyelitis, but we do not know with certainty that virus so killed will induce protection in the child even though it may induce antibodies. As implied by Dr. Evans, there are many possibilities to be seriously considered.

The profession is indebted to Dr. Evans for bringing into the open some of the possible hazards and limitations of the poliomyelitis vaccine in the face of the wide publicity that failed to mention them.

MEDICINE IN SOUTH AFRICA

Under the editorship of Prof. G. A. Elliott, Prof. J. Gillman, Prof. R. H. Goetz, Dr. J. Gear, Dr. Eric Samuel and Dr. A. Shedrow, a supplement to Volume 152 of *Acta Medica Scandinavica* has been issued.

This distinguished contribution to clinical journalism in South Africa is sponsored by the South African Council for Exchange of Medical Sciences. It will be reviewed in a forthcoming issue of this journal.

Copies (10s. 6d. each) may be obtained from the Eagle Press Ltd., P.O. Box 2878, Johannesburg.

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P.36

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FEWER SIDE EFFECTS induced by POLYCYCLINE than by either analogue. An important clinical advantage in the use of Polycycline is the greatly reduced frequency and severity of such reactions as nausea, vomiting, and diarrhoea —which so often necessitate termination of treatment with older broad-spectrum antibiotics.

MORE EFFICIENT ANTIBIOTIC ACTION WITH POLYCYCLINE than with older analogues chlortetracycline and oxytetracycline. Polycycline is more soluble than chlortetracycline and is thus more rapidly absorbed and more widely diffused throughout the body. And, because Polycycline is also more stable in solution than either analogue, higher serum concentrations are achieved, even in the spinal fluid, and these levels are maintained for a longer time.

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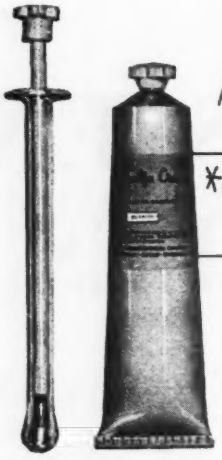

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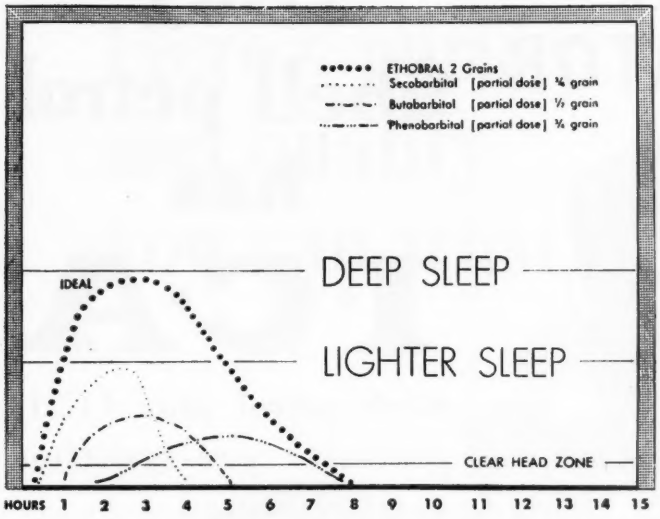
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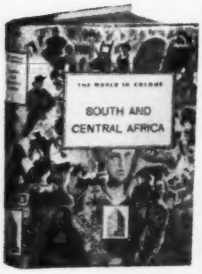

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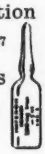

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